Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Regulatory Decision Document PRDD2005-03

Fenbuconazole

The technical grade active ingredient fenbuconazole and the associated end-use product, Indar 75 WSP Fungicide (contains fenbuconazole as active ingredient) for the control of blossom blight, fruit brown rot and black knot on stone fruit group (apricot, sweet cherry, tart cherry, nectarine, peach, plum, chickasaw plum, damson plum, Japanese plum and fresh prune) are proposed for full registration under the Pest Control Products Regulations.

This Proposed Regulatory Decision Document provides a summary of data reviewed and the rationale for the proposed registration of these products. The Pest Management Regulatory Agency (PMRA) will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications at the address below.

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Foreword

The submission for full registration of the active ingredient (a.i.) fenbuconazole and the end-use product Indar 75 WSP Fungicide developed by Dow AgroSciences Canada Inc. for the control of blossom blight, fruit brown rot and black knot on stone fruit group (apricot, sweet cherry, tart cherry, nectarine, peach, plum, chickasaw plum, damson plum, Japanese plum and fresh prune), has been reviewed by Health Canada's Pest Management and Regulatory Agency (PMRA) of Health Canada.

The PMRA had previously issued a temporary registration (Regulatory Note REG2003-03, *Fenbuconazole*) for these products with the requirement that Dow AgroSciences Canada Inc. carry out additional studies (including a validated method for animal biota and studies on the toxicity to beneficial predators and beneficial parasites). These data gaps were addressed satisfactorily, and this document details the scientific rationale used to support these products.

The PMRA has carried out an assessment of available information in accordance with the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value of the active ingredient fenbuconazole and the end-use product Indar 75 WSP Fungicide. The Agency has concluded that the use of the active ingredient fenbuconazole and the end-use product Indar 75 WSP in accordance with the label has merit and value consistent with the Pest Control Products Regulations and does not entail an unacceptable risk of harm. Therefore, based on the considerations outlined above, the use of the active ingredient fenbuconazole and the end-use product Indar 75 WSP Fungicide, for the control of blossom blight, fruit brown rot and black knot on stone fruit group (apricot, sweet cherry, tart cherry, nectarine, peach, plum, chickasaw plum, damson plum, Japanese plum and fresh prune) is proposed for full registration pursuant to the Pest Control Products Regulations.

Methods for analyzing fenbuconazole residues in various environmental media can be provided to monitoring agencies and research institutions upon request to the PMRA.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

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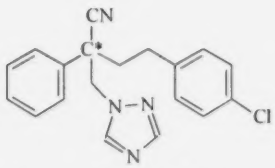
1.0 The Active Substance, its Properties and Uses

1.1 Identity of the Active Substance and Preparation Containing it

Active substance		Fenbuconazole
Function		Fungicide
Chemical name		
1.	International Union of Pure and Applied Chemistry (IUPAC)	(RS)-4-(4-chlorophenyl)-2-phenyl-2-(1*H*-1,2,4-triazole-1-ylmethyl)butyronitrile The active substance is a recemic mixture of R and S isomers. The IUPAC name is from ISO 1750:1981/DAM 2 document.
2.	Chemical Abstracts Service (CAS)	α-[2-(4-chlorophenyl)ethyl]-α-phenyl-1*H*-1,2,4-triazole-1-propanenitrile
CAS number		119611-00-6, racemate. This number supersedes 114369-43-6, but both are correct.
Molecular formula		$C_{19}H_{17}ClN_4$
Molecular weight		336.83
Structural formula		 *denotes chiral carbon
Nominal purity of active		98.7%, nominal (label and SPSF) (limits 95.8%, 99.5%)
Identity of relevant impurities of toxicological, environmental or other significance		The technical grade fenbuconazole does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances.

1.2 Physical and Chemical Properties of Active Substances and End-use Product(s)

Table 1.2.1 Technical Product—Fenbuconazole

Property	Result	Comment
Colour and physical state	Off-white to white powder	
Odour	Faintly sulphur-like	
Melting point or range	126.5–127.0°C	
Boiling point or range	Not required	
Density	0.50 g/mL, bulk density	
Vapour pressure at 25°C (pure active ingredient)	0.37×10^{-7} mm Hg (4.9×10^{-6}Pa)	The active ingredient will be non-volatile under field conditions.
Henry's Law constant at 20°C	4.3×10^{-9} atm·m^3/mol or 5.57×10^{6} (1/H)	The active ingredient will be non-volatile from moist soils or water.
Ultraviolet (UV)—visible spectrum	**λ max (nm)** — **ϵ (L·mol^{-1}·cm^{-1})** 196 — 53,000 262 — 750 268 — 740 275 — 480	The active ingredient has a low potential for ultraviolet light-induced phototransformation under normal environmental conditions.
Solubility in water at 22°C	**pH** — **Solubility (mg/L)** Not provided — 3.8	The solubility of the active ingredient in water is classified as low.
Solubility (g/L) in organic solvents at 25°C	**Solvent** — **g/100 mL** Acetonitrile — 23.1 Aromatic 200 — 7.7 Cyclohexanone — 44.5 Ethyl acetate — 15.9 Ethyl alcohol — 3.9 Heptane — 0.1 1-octanol — 1.3	

Property	Result	Comment
n-octanol–water partition coefficient (K_{ow}) (pure active ingredient, 99.5%)	1700 ± 300 log K_{ow} = 3.22 ± 0.08	There is potential for the active ingredient to bioaccumulate.
Dissociation constant (pK_a)	Not expected to dissociate in water.	
Stability (temperature, metal)	Stable to temperatures of 220°C or higher. Stable when exposed to stainless steel and aluminum metal and to potassium ions and iron (II) and iron (III) oxide.	

Table 1.2.2 End-use Product—Indar 75 WSP Agricultural Fungicide

Property	Result
Colour	Off-white
Odour	Musty, pungent
Physical state	Powder
Formulation type	Wettable powder
Guarantee	Fenbuconazole: 75.0%, nominal (label and SPSF) (limits 72.8%, 77.3%).
Formulants	The product does not contain any United States Environmental Protection Agency (USEPA) List 1 formulants or formulants known to be TSMP Track 1 substances.
Container material and description	Water soluble pouch with an outer waterproof bag.
Bulk density	Loose 0.16 g/mL Packed 0.20 g/mL
pH of 1% dispersion in water	7.6
Oxidizing or reducing action	None of the components is an oxidizing or reducing agent.

Property	Result
Storage stability	No significant change in level of active ingredient or in properties after 24 months' storage in commercial packaging (water soluble PVA bag), at 25°C.
Explodability	RH-7592 technical may undergo a dust explosion. K_{st} for technical RH-7592 is 265 bar-m/sec and minimum O_2 required for combustion is 12%. The RH-7592 75 WP explosion hazard is expected to be no greater than the technical.

1.3 Details of Uses

Indar 75 WSP is proposed for application to stone fruit (Use-site Category [USC] 14) to control the following:

- blossom blight and fruit brown rot of apricot, sweet cherry and tart cherry, nectarines, peaches and plums;
- leaf spot of sweet cherry and tart cherry;
- scab of peach; and
- black knot of sour cherry and plum.

The proposed use rate is 140 g product/500 L water/ha applied by ground (usually airblast) sprayer, with up to two sprays at early red bud stage through bloom stage, and a third coverspray pre-pick if needed. In addition it can be applied to fruit up to the time of harvest but not after harvest, and may be applied to foliage postharvest for leaf spot only. Spray water volume varies considerably with size of trees and is calculated case-by-case to give optimal coverage while maintaining product rate per hectare.

Indar 75 WSP should be first applied prior to infection. It is proposed at spray intervals of 7–14 days, depending on disease pressure, and can be applied up to the day of harvest. The applicant has indicated that there can be up to eight spray dates per season; however, the typical number of applications is two per disease.

2.0 Methods of Analysis

2.1 Method for Analysis of the Active Substance as Manufactured

Table 2.1.1 Method for Analysis of the Active Substance as Manufactured

Product	Analyte	Method ID	Method Type	Linear Range (%)	Relative Standard Deviation (RSD) (%)	Method Acceptability
Technical	Fenbuconazole	91-100-01	Cap GC	55–105	0.4	Y
Technical	Major impurities	91-100-01	Cap GC	0.1–1.0	2.5–10	Y

2.2 Method for Formulation Analysis

Table 2.2.1 Method for Formulation Analysis

Product	Analyte	Method ID	Method	Mean Recovery (%)	Relative Standard Deviation (%)	Method Acceptability
Indar 75 WSP	Fenbuconazole	92-119-01	GC	100.1% (n = 2)	0.48% (n = 6)	Acceptable

2.3 Methods for Residue Analysis

2.3.1 Multiresidue Methods for Residue Analysis

Existing multiresidue methods of analysis that are currently in common usage were not found to be suitable for the determination of fenbuconazole in stone fruit (apricot, cherry, nectarine, peach, plum and prune).

2.3.2 Methods for Residue Analysis of Plants and Plant Products

The residue of concern was defined as fenbuconazole (RH-7592) and its lactone metabolites (RH-9129 and RH-9130). The petitioner is proposing a single, specific, analytical method (TR 34-90-47R) for supervised residue trials and enforcement of maximum residue limit (MRL). This method can individually determine the residue of RH-7592, RH-9129 and RH-9130 in stone fruit matrices.

The residues of fenbuconazole and its lactone metabolites are extracted in stone fruits using methanol. The extract is separated by filtration and then partitioned with 9.1% sodium chloride and methylene chloride. The eluate is collected, evaporated to dryness and residues are reconstituted in toluene–acetone (100:10, v:v). Further purification is achieved using silica gel and florisil column chromatography with toluene–acetone (100:30, v:v) as the eluent. The residue is collected, evaporated to dryness, redissolved in toluene–methanol (100:3, v:v) and then analyzed by gas liquid chromatography using capillary column and thermionic specific detector optimized for nitrogen selectivity. The limit of detection (LOD) for fenbuconazole (RH-7592) and the metabolites (RH-9129 and RH-9130) was established at 0.01 ppm in stone fruit. The limit of quantification (LOQ) for fenbuconazole (RH-7592) and the lactone metabolites (RH-9129 and RH-9130) was established at 0.05 ppm in stone fruit.

The method validation recoveries were adequate in stone fruit matrices when samples were spiked with a mixture of analytes at levels of 0.01 to 4.0 ppm. The recoveries were 89 ± 6% for RH-7592, 90 ± 6% for RH-9130 and 82 ± 10% for RH-9129. The method/detector response for all analytes was linear over the range of 0.05–1.0 ppm with a correlation coefficient of >0.999. The method applied external standards as markers for retention time, response and calibration. The chromatographic peaks were well defined and symmetrical with no apparent carryover to the subsequent chromatograms in the area of analytical interest for both control and spiked samples.

The independent laboratory validation did support the reliability and reproducibility of the analytical method for the determination of the residues of the RH-7592, RH-9129, and RH-9130 in stone fruit matrices. When samples were spiked with a mixture of analyte at 1.0 ppm and 2.0 ppm, recoveries were 97 ± 5% for RH-7592, 94 ± 5% for RH-9130 and 90 ± 6% for RH-9129 in stone fruit matrices.

2.3.3 Methods for Residue Analysis of Food of Animal Origin

Neither poultry nor livestock feed items are associated with the use of fenbuconazole on stone fruit. Therefore, no analytical method is needed for animal commodities.

2.3.4 Methods for Residue Analysis of Soil

The major residues in soil are fenbuconazole (RH-7592), its lactones (RH-9129 and RH-9130) and ketone [RH-6467, 4-(4-chlorophenyl)-2-(methyl-1*H*-1,2,4-triazole)-4-oxo-2-phenylbutanenitrile] transformation products. The applicant has provided a method to analyze all four chemicals. The sample was blended with methanol and Celite 545 then filtered. After adding sodium chloride, it was extracted with methylene chloride; the residue was dissolved in toluene–acetone (100:10), cleaned up with a silica solid phase extraction column and eluted with toluene–acetone (100:50). The eluate was evaporated and the residue in toluene–methanol (100:3) was analyzed by gas chromatographic method with thermionic specific detector. The method showed good linearity range

(0.05–0.5 ppm), precision (RSD = 9.6% for RH-7592, 13.2% for RH-9129, 13.5% for RH-9130 and 14.9% for RH-6467), accuracy (mean recoveries = 94.6% for RH-7592, 96.8% for RH-9129, 96.7% for RH-9130 and 101.7% for RH-6467, n = 78), sensitivity (LOQ = 0.01 ppm for all analytes) and specificity (absence of interferences around the retention vicinity of the analytes in the chromatograms of control samples).

2.3.5 Methods for Residue Analysis of Water

The applicant has provided a method using gas chromatography with thermionic specific detector for the determination of the parent compound (RH-7592) in tap water. Water sample was filtered, passed through a C18 extraction disk that was then pulled dried by air. The disk was eluted with ethyl acetate; the eluate was evaporated at 70˚C and the residue reconstituted in toluene/methanol (100:3) and analyzed for the parent compound. The method showed good precision (RSD = 14%), accuracy (mean recovery = 98%, n = 10), sensitivity (LOQ = 0.1 ppb) and specificity (absence of interferences around the retention vicinity of RH-7592).

2.3.6 Methods for Residue Analysis of Animal Biota

The major residues in animal matrix are fenbuconazole (RH-7592) and its lactones (RH-9129 and RH-9130) transformation products. The applicant has provided a method to analyze all three chemicals. The meat sample was homogenized with dry ice which was then allowed to sublime overnight in a freezer. Milk and egg samples were blended with methanol. The sample was partitioned with water, methanol and hexane. Sodium chloride was added to the aqueous phase that was then partitioned with methylene chloride. The methylene chloride was separated, evaporated to dryness. The residue was cleaned up with silica gel column followed by C18 solid phase extraction (SPE) column, then florisil column. The eluate from the SPE column was analyzed for RH-7592, RH-9129 and RH-9130; the eluate from Florisil column was analyzed RH-7968 by a gas chromatographic (GC) method with thermionic specific detector. For cow and hen muscles, the method showed good linearity range (0.01–1 µg/mL), precision (RSD 8.2% for RH-7529, 8.9% for RH-9129 and 11.5% for RH-9130), accuracy (mean recovery = 95.8 ± 7.9% for RH-7529, 101.71 ± 9.1% for RH-9129 and 104.2 ± 12.1% for RH-9130, n = 18), sensitivity (LOQ = 0.01 ppm for all three compounds) and specificity (all three peaks well separated in the chromatograms of fortified control sample and sample).

3.0 Impact on Human and Animal Health

3.1 Integrated Toxicological Summary

A detailed review of the toxicology database available for the new fungicide, fenbuconazole, has been completed. Data submitted were complete and well presented, and included the full battery of studies currently required for registration purposes. The

submitted studies were conducted in conformance with currently acceptable international testing protocols.

Following oral dosing, ^{14}C-RH-7592 was rapidly absorbed, distributed and excreted. The feces was the major route of excretion accounting for ~76% to 94% of the administered dose. Recovery from urine ranged from ~5% to 14%. The majority of the radioactivity was excreted within 24 to 48 hours postdosing. Biliary excretion data indicated that systemic absorption of RH-7592 was high for all dosing groups. Tissue distribution and bioaccumulation were minimal, with <1% of the administered dose recovered in tissues at 96 hours. There was no sex- or dose-related differences in absorption, distribution or elimination.

There were many metabolites in excreta indicating extensive metabolic breakdown. All major metabolites were derived from enzymatic oxidations on either the benzylic carbon alpha to the chlorophenyl ring or the 3- or 4- position of the phenyl ring. Subsequent non-enzymatic cyclization of the newly formed benzylic alcohol with the adjacent nitrile group, followed by hydrolysis led to the iminolactone/lactone family of metabolites. Conjugation of the OH groups of the alcohol and phenols led to more metabolites, as did combinations of the above-mentioned reactions. A minor metabolic pathway was the cleavage of RH-7592 to yield triazole and RS-5922. There was no significant difference in the total metabolite profile for male and female rats, although some metabolites were present in greater quantities in males, and vice versa. There was a dose-related difference in metabolism, with a higher amount of unmetabolized parent compound in the feces of the high-dose group, compared to the low-dose and repeated-dose groups, indicating that saturation of the metabolic pathway may be occurring at the high dose.

Acute dosing revealed that technical fenbuconazole was of low toxicity by the oral, dermal and inhalation routes. It was non-irritating to the skin, minimally irritating when instilled into the eyes and was not a skin sensitizer (Buehler method). The Indar 75WP formulation, containing 77.5% fenbuconazole, was of low toxicity by the oral, dermal, and inhalation routes. It was minimally irritating to the skin and eyes and was not a dermal sensitizer (Buehler method).

Short-term (28 days) repeated dermal dosing in rats with technical fenbuconazole did not result in any treatment-related systemic or dermal effects up to and including the highest dose level tested (limit dose) of 1000 mg/kg bw/day.

The target organ for all species tested, after both short-term and long-term exposure to technical fenbuconazole, was the liver. Liver weights were increased at dose levels of ~13 mg/kg bw/day and higher for dogs, and ~25 mg/kg bw/day and higher for mice and rats, with corresponding histopathological changes (hepatocyte hypertrophy and vacuolization in all 3 species; hepatocyte hyperplasia and necrosis in mice only). In addition, male rats exhibited hepatocyte vacuolation at ~5 mg/kg bw/day. Increased liver enzyme activity was observed for mice (SGOT, SGPT) and dogs (alkaline phosphatase,

SGPT, SGOT). The thyroid was also a target organ for rats, with increased thyroid weight, follicular cell hypertrophy and focal cystic hyperplasia observed at doses of ~30 mg/kg bw/day and higher. In addition, plasma thyroxine was decreased and thyroid stimulating hormone (TSH) was increased at a dose of 62.07 mg/kg bw/day. Thyroid weight and adrenal weight were increased for dogs at ~45 mg/kg bw/day but without corresponding histopathological findings.

There was evidence of oncogenic/carcinogenic potential of fenbuconazole in rodents. For rats, there was an increased occurrence of thyroid follicular cell benign tumours and combined thyroid follicular cell benign and malignant tumours in males (28.87 mg/kg bw/day). For mice, this was based on the occurrence of an increased trend for malignant liver tumours in males (85.26 mg/kg bw/day) and an increase in benign liver tumours and combined benign and malignant liver tumours in females (208.84 mg/kg bw/day). The proposed mechanism of action for the thyroid tumours in rats was scientifically supported by sound mechanistic data, i.e., prolonged stimulation of the thyroid by TSH leads to chronic follicular hypertrophy/hyperplasia, progressing to follicular neoplasia of the thyroid. However, data submitted for the proposed mechanistic pathway for liver tumours in mice did not provide a convincing hypothesis. The in vitro and in vivo mutagenicity assays conducted yielded negative results for genotoxic potential. In addition, two metabolites of fenbuconazole, i.e., RH-99129 and RH-99130, were negative for genotoxicity when tested according to the *Salmonella*/Ames Assay. It is therefore recommended that for the purpose of risk characterization a low-dose extrapolation model be applied for human risk (Q_1*). This decision is based on the induction of liver carcinomas in male mice. The Q_1* for fenbuconazole is 1.54×10^{-2} (mg/kg bw/day)$^{-1}$ in human equivalents.

Reproductive performance, maternal toxicity and offspring toxicity in rats were seen only at the high dose of 66.4 mg/kg bw/day. Reproductive findings were as follows:

- decreased number of dams delivering;
- decreased litter size;
- decreased number and percentage of dams with liveborn pups;
- decreased gestation index;
- increased number and percentage of dams with stillborn pups; and
- increased number of litters with no viable offspring (P_1 only).

Offspring effects were decreased pup viability and lower pup body weight on days 0, 4, 7, 14 and 21 postpartum for the F_1 pups. Parental findings were as follows:

- treatment-related mortality in females only;
- decreased mean body weight, body-weight gain and food consumption; increased liver weights;
- hepatocyte vacuolation and hypertrophy;
- increased thyroid weight in males only; follicular cell hypertrophy in both sexes;
- increased adrenal weight in females only; and
- hypertrophy of the zona glomerulosa in both sexes.

Increased susceptibility of pups was not demonstrated in this study.

Fenbuconazole was not teratogenic to rat or rabbit fetuses at dose levels up to and including 150 mg/kg bw/day (rats) and 30 mg/kg bw/day (rabbits). A meaningful evaluation of soft tissue, visceral or skeletal effects could not be conducted for rabbits in the high dose (60 mg/kg bw/day) group (maternally toxic dose level) because only one litter was produced. Developmental toxicity was noted for rats at 75 and 150 mg/kg bw/day (maternally toxic doses), manifested as a decrease in the number of live fetuses/litter and an increase in postimplantation loss. In addition, there was an increase in early and late resorptions in the 150 mg/kg bw/day group. Fetotoxicity was evident as an increased incidence of incompletely ossified or unossified sternebrae noted for rat fetuses in the 75 and 150 mg/kg bw/day groups and an increased incidence of rudimentary 14th ribs and partially or unossified pubes in the 150 mg/kg bw/day group. These minor variations were not considered to be adverse, toxicologically significant findings. For rabbits, embryo-fetal mortality (abortions, total resorptions of litters) was observed at 60 mg/kg bw/day (maternally toxic dose). Maternal findings were observed in rabbits at 30 and 60 mg/kg bw/day (decreased food intake, clinical findings at 30 and 60 mg/kg bw/day; loss of body weight, increased mortality at 60 mg/kg bw/day). Maternal toxicity was seen in rats at 75 and 150 mg/kg bw/day (clinical signs, lower body-weight gain and lower gravid uterus weight). There was no evidence for increased susceptibility of rat or rabbit fetuses following in utero exposure to fenbuconazole.

3.2 Determination of Acceptable Daily Intake

The lowest no observed effect level (NOEL) was 10 ppm, equal to 1.28/1.59 mg/kg bw/day, established in the 78-week oncogenicity feeding study in mice, based on increased liver weight and liver histopathology at higher dose levels. For the calculation of the acceptable daily intake (ADI), an uncertainty factor (UF) of 100 is proposed. This provides a margin of safety (MOS) of 500× for reproductive toxicity.

The ADI proposed is calculated according to the following formula:

$$ADI = \frac{NOAEL}{SF} = \frac{1.28 \text{ mg/kg bw/day}}{100}$$

$$= 0.0128 \text{ mg/kg bw/day of fenbuconazole.}$$

3.3 Acute Reference Dose

For an acute reference dose (ARfD) for females 13+ years of age, the studies considered most appropriate in the submitted toxicological data base are the rat and rabbit teratology studies. The dose and endpoint selected for risk assessment is 30 mg/kg bw/day (decrease in live fetuses per litter, and an increase in postimplantation loss at 75 and 150 mg/kg bw/day for rats; increase in abortions and postimplantation loss at 60 mg/kg bw/day for

rabbits). For the calculation of the ARfD, an uncertainty factor of 300 is proposed. This is based on the standard uncertainty factor of 100 with an additional 3-fold uncertainty factor due to the severity of the toxicological endpoint, i.e., increased postimplantation loss and a decrease in the number of live fetuses per litter.

The ARfD proposed is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{SF}} = \frac{30 \text{ mg/kg bw/day}}{300}$$

$$= 0.10 \text{ mg/kg bw/day of fenbuconazole}$$

3.4 Toxicology Endpoint Selection for Occupational and Bystander Risk Assessment

For mixers, loaders and applicators treating stone fruits, the expected duration of exposure, which is predominantly via the dermal route, is intermittent over a 4-month period. For re-entry workers, the expected duration of exposure is intermittent to continuous, intermediate-term (i.e., <6 months). Re-entry exposure would be dermal.

Adequate dermal toxicity data of sufficient duration for the requested orchard use were not available for INDAR 75 WSP. Oral studies of sufficient duration have been used for the assessment of risk. After 3 months of dietary exposure to fenbuconazole, a NOAEL of 1.3 mg/kg bw/day (rat) was determined, based on hepatocyte vacuolation at the next dose of 5.1 mg/kg bw/day. The NOAEL established in this study was considered the most appropriate toxicological endpoint for use in the occupational risk assessment.

Maternal toxicity (NOAEL: 10 mg/kg bw/day; rabbit), reproductive toxicity (NOAEL: 6.4 mg/kg bw/day; rat) and developmental toxicity (NOAEL: 30 mg/kg bw/day; rabbit, rat) concerns have been adequately addressed with the NOAEL of 1.3 mg/kg bw/day from the 3-month dietary study (rat).

As fenbuconazole did not demonstrate toxicity concerns on genotoxicity, teratogenicity, or neurotoxicity, the target margin of exposure is 100 for interspecies and intraspecies variation. There was no evidence of increased sensitivity of the young.

There is evidence of carcinogenicity in animals following long-term exposure to fenbuconazole. It is recommended that, for the purpose of risk characterization, a low-dose extrapolation model be applied for human risk (Q_1^*). This decision is based on the induction of liver carcinomas in male mice. The Q_1^* for fenbuconazole is 1.54×10^{-2} $(\text{mg/kg bw/day})^{-1}$ in human equivalents.

3.5 Impact on Human and Animal Health Arising from Exposure to the Active Substance or to its Impurities

Indar 75 WSP would be applied at a rate of 105 g a.i./ha by airblast equipment, up to 8 times per season. A mixer/loader/applicator (farmer) would typically treat 30 ha of stone fruits per day. At each application, applicators would handle 3.15 kg a.i. There is potential for intermittent exposure to farmers over a four-month period.

Workers re-entering treated areas will have potential for postapplication exposure. Application times coincide with pruning, hand thinning, harvesting and other re-entry activities in orchards. There is potential for intermittent to continuous, intermediate-term dermal exposure for re-entry workers.

Dermal Absorption

The dermal absorption of ^{14}C RH-7592 (fenbuconazole) was determined in male rats at doses of 0.002, 0.027 and 1.98 mg/cm^2. Exposure durations were 0.5, 1, 2, 4, 10 and 24 hours, 4 rats per dose duration. In addition, one group of animals in the 0.002 mg/cm^2 dose groups was exposed for 10 hours and then sacrificed after 168 hours (7 days). Recovery at all doses ranged from 73 to 111% of the administered dose.

Absorption was low and increased with duration of exposure. The maximum dermal absorption occurred at the low dose (0.002 mg/cm^2). Due to the limitations of the study, particularly the uncertainties regarding the applicability of the study formulations to the proposed product formulation, the highest dermal absorption value from the 0.002 mg/cm^2 dose group (i.e., 12% at 24 hours) was considered to be the most appropriate value to use for exposure assessments. As the study design did not permit analysis of the fate of skin-bound residues, this dermal absorption value includes residues retained at the skin site (approximately 4%).

3.5.1 Operator Exposure Assessment

Mixer/loader/applicator exposure was estimated using the Pesticide Handlers' Exposure Database Version 1.1 (PHED 1.1). The PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates. With a few exceptions as noted, the PHED estimates meet criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides. Exposure via the inhalation route was a minor component of overall exposure and was added to the dermal deposition estimates coupled with a default dermal absorption value of 12%.

To estimate exposure for each use scenario, appropriate subsets of A- and B-grade datasets were created from the mixer/loader/applicator database files of PHED. All data were normalized for kg of active ingredient handled. Exposure estimates are presented on

the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part. Estimates were derived for individuals wearing one layer of clothing and gloves during mixing, loading and application.

The following exposure estimates and margins of exposure and cancer risk were derived for mixer/loader/applicators:

Table 3.5.1 Mixer/Loader/Applicator Exposure

Occupational Scenario	Exposure [1] (mg/kg bw/day)	Margin of Exposure [2]	LADD[3] (mg/kg bw/day)	Cancer Risk[4]
Mixer/Loader + Applicator Exposure [5]				
Stone Fruit—airblast	0.00342	380	4.00×10^{-5}	6.16×10^{-7}

1 Based on a 70 kg operator, typical North American use patterns of 30 ha/day for stone fruit, and 12% default dermal absorption

2 Based on NOAEL 1.3 mg/kg bw/day from a 3-month oral rat study

3 Lifetime average daily dose, calculated assuming 8 days of exposure per year, a life expectancy of 75 years, and a working lifetime of 40 years.

4 Based on Q_1^* of 1.54×10^{-2} $(mg/kg\ bw/day)^{-1}$

5 Individuals wearing one layer of clothing and gloves (exception: groundboom applicator not wearing gloves)

These margins of exposure and cancer risk are acceptable.

3.5.2 Bystanders

Given that the application is restricted to agricultural areas, and that the product would be applied using ground equipment only, exposure and risk to bystanders is expected to be negligible. In addition, a statement will be added on the label that the product is not for use on residential properties.

3.5.3 Workers

Re-entry activities include pruning, thinning and hand-harvesting of fruit as well as other pesticide applications. Some of these activities may involve considerable contact with the treated foliage and may coincide with the timing of application of Indar 75 WSP.

In the absence of data, a Tier 1 assessment of re-entry exposure was conducted assuming that 20% of the application rate is dislodgeable and that dislodgeable foliar residues (DFRs) would dissipate at a rate of 10% per day. In addition, for multiple applications, residues were assumed to be cumulative (i.e., any residue remaining before the next application was added and each application was assumed to add the same DFR as the first application). In order to derive an estimate of dermal exposure, the estimated DFR data

are coupled with generic transfer coefficients appropriate for re-entry activities conducted in stone fruit orchards. The applicant, Dow AgroSciences Canada Inc., is a member of the Agricultural Re-entry Task Force (ARTF), and as such, the transfer coefficient of 3000 cm^2/hr for thinning and harvesting, generated from a study sponsored by the ARTF, was used. Thinning and harvesting is considered to be the activity with the highest potential for dermal exposure. Assuming an 8-hour workday and a body weight of 70 kg, dermal deposition of fenbuconazole each day after application was calculated using the following equation:

$$\text{Dermal deposition (mg/kg bw/day)} = \frac{\text{TC } (cm^2/hr) \times \text{DFR } (\mu g/cm^2) \times 8 \text{ hr}}{70 \text{ kg bw}} \times \frac{1 \text{ mg}}{1000 \ \mu g}$$

To estimate the dermally absorbed exposure, a dermal absorption factor of 12% was applied.

Re-entry exposure estimates for the various stone fruit crops were derived based on the proposed spray schedule for use of Indar 75 WSP on stone fruit in Canada. Indar 75 WSP could potentially be applied up to 7 applications/season; however, it is unlikely that the product would be applied at every one of those stages, since the typical number of applications to each crop would be approximately 3 or 4. It is assumed that the growing season of peaches, apricots, and nectarines would be 120 days (4 months) and of cherries, 100 days. It is also assumed that re-entry exposure would occur every day during the growing season. The daily time-weighted average exposure, margins of exposure, lifetime average daily dose (LADD) and cancer risk for re-entry workers are presented in Table 3.5.3.

For re-entry workers, MOEs ranged from 200 to 300. These are considered to be acceptable.

Cancer risks ranged from 8×10^{-6} to 1×10^{-5}. These cancer risks are considered acceptable in light of the conservatisms in the exposure assessment. These conservatisms include the following:

- The assumption that the maximum number of applications per year would be applied, when according to typical practices, applications would be 3 to 4 per year.
- The assumption that exposure would occur every day during the growing season (up to 4 months) and that workers would work 8 hours per day for that duration of time.
- Use of the highest transfer coefficient for thinning and harvesting.
- Based on acute toxicity data of fenbuconazole (Toxicity Category IV), a restricted entry interval of 12 hours must be specified on the label.

Table 3.5.3 Re-entry Exposure from Use of Indar 75 WSP on Stone Fruit

Crop	Daily Time-weighted Average Exposure[2] (μg/kg bw/year)	Margin of Exposure[3]	LADD[4] (mg/kg bw/day)	Cancer Risk[5]
Peaches	4.23	300	7.43×10^{-4}	1×10^{-5}
Apricots Nectarines Peaches	2.8	500	4.90×10^{-4}	8×10^{-6}
Cherries	6.04	200	8.83×10^{-4}	1×10^{-5}

1 Assuming the growing season is days 1 to 120 (peaches, apricots, nectarines), or days 1 to 100 (cherries).
2 Including 12% dermal absorption.
3 Based on NOAEL 1.3 mg/kg bw/day from a 3-month oral rat study
4 Lifetime average daily dose, calculated assuming 100 or 120 days of exposure per year, a life expectancy of 75 years, and a working lifetime of 40 years.
5 Based on Q_1^* of 1.54×10^{-2} $(mg/kg\ bw/day)^{-1}$

NOTE: Postapplication estimates for plums were not determined because it was assumed to be covered off by other crops.

3.5.4 Consumers

Not applicable.

4.0 Residues

4.1 Food Residues Exposure Assessment

Nature of the Residue in Plants

Fenbuconazole (RH-7592, 6.8% a.i. emulsifiable concentrate) radiolabelled as phenyl-[^{14}C]RH-7592 or triazole-[^{14}C]RH-7592 was applied 5 times at a rate of 200 g a.i./ha (1 kg a.i./ha/season) on peach trees. In the experiments conducted with phenyl-labelled RH-7592, the parent compound (RH-7592) and the lactone metabolite (RH-9129) were the only two compounds identified. These compounds were present at residue levels of 0.036 ppm and 0.011 ppm, respectively. Since the lactone metabolite contains two asymmetric carbons, it can exist in the form of two stereoisomers. The other stereoisomer of lactone metabolite, RH-9130, was not identified in any peach metabolism sample. The glucose conjugates of RH-4911 were also found at levels of 0.006 ppm. In the experiments conducted with triazole-labelled RH-7592, triazole alanine (RH-3968) and parent compound (RH-7592) were predominant residues found at levels of 0.062 ppm and 0.020 ppm, respectively. The lactone metabolite (RH-9129) and triazole acetic acid (RH-4098) at levels <0.01 ppm were also identified. Based on the peach metabolism

study, the residue of concern is defined as the parent RH-7592 and its lactone metabolites, RH-9129 and RH-9130.

Confined Accumulation in Rotational Crops
Stone fruits are perennial crops. No other food or feed crop is grown in a stone fruit orchard. Therefore, there is no concern for secondary residues in any other food or feed.

Field Accumulation in Rotational Crops
Stone fruits are perennial crops. No other food or feed crop is grown in a stone fruit orchard. Therefore, there is no concern for secondary residues in any other food or feed.

Nature of the Residue in Animals
No poultry or livestock feed item is associated with the use of fenbuconazole on stone fruit. Therefore, no animal metabolism study is needed.

Methods for Residue Analysis of Food of Animal Origin
No poultry or livestock feed item is associated with the use of fenbuconazole on stone fruit. Therefore, no analytical method for animal commodities is needed.

Methods for Residue Analysis of Plants and Plant Products
The analytical method (TR 34-90-47R) was proposed for supervised residue trials and tolerance enforcement. This method determines fenbuconazole (RH-7592) and its metabolites (RH-9129 and RH-9130) by gas liquid chromatography using capillary column and thermionic specific detector. The LOD for RH-7592, RH-9129 and RH-9130 in stone fruit was established at 0.01 ppm. The LOQ for the RH-7592, RH-9129 and RH-9130 in stone fruit was established at 0.05 ppm. This method was found to give adequate recoveries in stone fruit matrices. The recoveries were 89 ± 6% for RH-7592, 90 ± 6% for RH-9130 and 82 ± 10% for RH-9129. The detector response for all analytes was linear over the range of 0.05–1.0 ppm. The independent laboratory validation of method supported the reliability and reproducibility of the analytical method to determine the residue of fenbuconazole and its metabolites in stone fruit matrices.

Storage Stability Data
Samples of stone fruits spiked with fenbuconazole (RH-7592) and its metabolites (RH-2930 and RH- 2929) at a level of 0.5 ppm were stored at approximately -10°C for a duration of up to 54.5 months. All samples were analyzed at 0, 92, 182, 214, 365, 555, 723, 909, 1088, 1263, 1471 and 1634 days of freezer storage. Residues of fenbuconazole (RH-7592) and metabolites (RH-9129 and RH-9130) were stable in stone fruits at approximately -10°C up to 54.5 months.

Crop Field Trials
Supervised crop field trials were conducted on apricot, cherry, peach, plum, and fresh prune in the United States. Results indicated that maximum combined residues of fenbuconazole and the metabolites were in apricot 0.27 ppm, cherries 0.749 ppm, peaches

0.5 ppm, plum and prune 0.08 ppm, when plants were treated six to twelve times with fenbuconazole formulated as 2F or Indar 75 WSP at a rate of 672–1344 g a.i./ha/season (0.9–1.82 × proposed good agricultural practices [GAP]). The residue trials submitted for peaches are accepted as bridging data to support the use of Indar 75 WSP on nectarines.

Consequently, MRLs in/on apricot (0.3 ppm), cherry (0.8 ppm), nectarine (0.5 ppm), peach (0.5 ppm), plum (0.1 ppm), fresh prune (0.1 ppm) and dry prune (0.5 ppm) are recommended to cover residues of RH-7592, RH-9129 and RH-9130.

Processed Food/Feed

Fenbuconazole (2F formulation; 23.5% a.i.) was applied to plum at a rate of 672 or 694 g a.i./ha (approximately 1× the proposed Canadian season rate). The fresh plums were processed into dry prunes. A comparison of the residues in the raw agricultural commodity (RAC) with those in processed fruit demonstrated concentration in dry prune. When treated according to the proposed Canadian use pattern, the concentration factor for dry prune is not expected to exceed 5. The residues of fenbuconazole and its lactone metabolites in dry prune will be covered under the recommended MRL of 0.5 ppm.

Meat/Milk/Poultry/Eggs

No poultry or livestock feed item is associated with the use of fenbuconazole on stone fruit. It is expected that no residue of fenbuconazole will be present in poultry and livestock food commodities as a result of this use.

Dietary Risk Assessment

The proposed domestic use of fenbuconazole on apricot, cherry, nectarine, peach, plum and prune does not pose an unacceptable chronic, acute, or lifetime dietary cancer risk from food and water to any segment of the population, including infants, children, adults, and seniors. The available refinements were used (Canadian Supervised Trial Median Residues [STMRs], American mean residue, processing study data, and estimated percent crop treated information). For chronic risk from dietary exposure to the residues of fenbuconazole and its metabolites from food and water, the potential daily intake (PDI) was less than 3% of the ADI for all population subgroups including infants, children, adults and seniors. For acute dietary intake at the 95th percentile, exposure to the residues of fenbuconazole and its metabolites represented less than 2% of the ARfD for the women 13+ years of age. The lifetime cancer risk from dietary exposure to the residues of fenbuconazole and its metabolites from food and water was estimated to be 1.72×10^{-6} for all infants (<1 year) and children 1–6 years as well as $< 8 \times 10^{-7}$ for the rest of the subgroups. It is expected that further refinement would result in a lifetime risk less than the level of concern of 1.00×10^{-6}.

5.0 Fate and Behaviour in the Environment

5.1 Physical and Chemical Properties Relevant to the Environment

Fenbuconazole has low solubility in water and is not expected to dissociate in water. The vapour pressure and Henry's Law constant indicate that fenbuconazole is non-volatile. Furthermore, fenbuconazole has a low potential for ultraviolet light-induced phototransformation under normal environmental conditions. The *n*-octanol–water partition coefficient is relatively high, indicating that there is potential for the active ingredient to bioaccumulate in organisms (Table 5.1.1). Data were not available on the physicochemical properties of environmental transformation products.

Table 5.1.1 Physical and Chemical Properties of the Active Ingredient Relevant to the Environment

Property	Value	Comments
Solubility in water	3.8 mg/L	The solubility of the active ingredient in water is classified as low.
Vapour pressure	0.37×10^{-7} mm Hg (0.005 mPa)	According to Kennedy and Talbert (1977), the active ingredient is non-volatile under field conditions.
Henry's Law constant	4.3×10^{-9} atm·m^3/mol or 5.57×10^{6} (1/H)	The active ingredient is non-volatile from water or moist soil.
Log K_{ow}	$K_{ow} = 1700 \pm 300$ $\log K_{ow} = 3.22 \pm 0.08$	There is potential for the active ingredient to bioaccumulate.
pK_a	No value provided	The active ingredient is not expected to dissociate in water.
UV—visible absorption	**λ max (nm)** **ε (L·mol^{-1}·cm^{-1})** 196 53 000 262 750 268 740 275 480	The active ingredient has a low potential for ultraviolet light-induced phototransformation under normal environmental conditions.

5.2 Abiotic Transformation

Laboratory studies on the hydrolysis, phototransformation on soil and phototransformation in water were submitted to determine the effect of abiotic processes on fenbuconazole.

In an hydrolysis study, the half-lives of fenbuconazole were extrapolated to 2210, 3740 and 1340 days (equivalent to 6.1, 10.2 and 3.7 years) at pHs 5, 7 and 9, respectively. This indicates that fenbuconazole is stable to hydrolysis at environmentally relevant pHs.

The phototransformation on soil was slow, with a half-life of 79 days under conditions of 12 hours light:12 hours dark. Only two unidentified minor transformation products were measured on soil reaching maxima of 3.03% and 2.75% of the applied radioactivity. Fenbuconazole did not phototransform in water. The half-life for phototransformation in water was estimated at 1280 days (~3.5 years) under conditions of 12 hours light to 12 hours dark. Transformation products were not detected in water. Phototransformation is not an important route of transformation of fenbuconazole on soil and is not a route of transformation in water. Data on the phototransformation in air were not required as volatilization is not expected.

Fenbuconazole does not undergo hydrolysis or photolysis in water; therefore, it can be considered to be stable to abiotic processes in water. Fenbuconazole undergoes very limited phototransformation on soil with two minor, unknown transformation products produced from this process; therefore, fenbuconazole is not subject to abiotic transformation mechanisms.

5.3 Biotransformation

Laboratory studies on the biotransformation of fenbuconazole in aerobic soil, anaerobic soil and aerobic water/sediment systems were reviewed to determine the effect of biotic (microbial) processes on fenbuconazole.

Biotransformation processes were examined in two aerobic soils. An average of 45.7% of the parent compound transformed under aerobic conditions between day 7 and day 363 of the study (silty clay loam: 53.6%; sandy loam: 37.6%). The half-lives were 258 days and 367 days in silty clay loam and sandy loam soils, respectively. The major transformation products detected were RH-9129 and free triazole in the silty clay loam, with major transformation products not detected in the sandy loam samples. Minor transformation products RH-9130 and RH-6467 were formed in silty clay loam, while in sandy loam, the minor transformation products were free triazole, RH-9129, RH-9130 and RH-6467, with high quantities (approximately 20%) of unidentified radioactivity (products). Biotransformation is a route of transformation of RH-7592 in aerobic soils, but this is a slow process. According to the classification scheme of Goring et al. (1975), fenbuconazole is persistent in soil under aerobic conditions.

The transformation of fenbuconazole was examined in two anaerobic soils. Following 30 days of aerobic aging, less than 3.2% of fenbuconazole had mineralized to CO_2. By the end of the study, 7.8% of the parent compound had transformed. The half-lives of fenbuconazole in anaerobic silty clay loam and sandy loam were 451 days and 655 days, respectively, exceeding the half-lives in aerobic soils. Major transformation products were not detected. The minor transformation products RH-9129, RH-9130 and RH-6467 were detected with high quantities of unidentified radioactivity. As only 7.8% of the parent compound transformed under anaerobic conditions after 60 days, biotransformation is a route of transformation in anaerobic soil; however, this is a very slow process. According to the classification scheme of Goring et al. (1975), fenbuconazole is persistent in soil under anaerobic conditions.

In a study on aerobic aquatic biotransformation, fenbuconazole strongly partitioned to sediment. For example, the concentration of fenbuconazole in river water decreased from 96% of the applied radioactivity (AR) at initiation to 3.6% AR after 105 days. As concentrations in water decreased, the concentration in sediments increased from 11% AR to 79% AR. A similar effect was observed in the pond system. Major transformation products were detected in neither water nor sediment. Naming/identification conventions were inconsistent and only certain transformation products were specifically identified as RH-6467 or RH-129/130 (also called RH-29/30 or RH-99129/RH-99130). The maximum dissipation times in water were 4.3 and 1.2 days in river and pond water, respectively. The study did not present dissipation times for sediment; however, for the entire system, the maximum DT_{50}s exceeded 1000 days. The results indicate faster dissipation of fenbuconazole in the pond system. This may be a direct consequence of the amount of total organic carbon (TOC) in the water as the pond water contained approximately twice the level of TOC as the river water. Thus, the study's author speculated that adsorption to suspended colloidal organic particles may be a process by which scavenging of fenbuconazole takes place. This process may augment partitioning to the sediment layer. Another explanation for the more rapid dissipation in the pond system may be that there is more microbial activity in pond water than in river water. Although transformation of fenbuconazole appeared to occur in water, aerobic biotransformation is not an important route of transformation in water/sediment systems. The primary route of dissipation of fenbuconazole in aerobic water/sediment systems is partitioning to sediment. According to the classification scheme of McEwen and Stephenson (1979), fenbuconazole is non-persistent in water and persistent in sediment.

A request for a waiver was granted in place of an anerobic sediment/water study as the aquatic biotransformation behaviour of RH-7592 under anaerobic conditions is described by other submitted studies.

Biotransformation is a route of transformation of fenbuconazole under aerobic and anaerobic conditions in soil, but this is a slow process. In aquatic environments, fenbuconazole appears to be rapidly removed from water; however, it does not undergo significant biotransformation in water/sediment systems. Rather, the compound is

partitioned to sediments, acting as a sink for this compound. Based on studies of biotransformation, according to the classification schemes of Goring et al. (1975) and McEwen and Stephenson (1979), fenbuconazole is persistent in soil and water/sediment systems (i.e., in the sediment portion). Major transformation products (RH-9129 and free triazole) were only detected in aerobic soils.

5.4 Mobility

The adsorption/desorption characteristics of fenbuconazole were studied in five types of soil from the United States by a batch equilibrium experiment. After 84 hours of equilibration, 86%, 80%, 74%, 62% and 48% of the applied RH-7592 was adsorbed in sandy loam, loam, silty clay loam, clay and sand, respectively. The adsorption K_d values ranged from 5.1 (clay) to 115 mL/g (sandy loam) with corresponding adsorption K_{oc} values ranging from 2185 (clay) to 9042 mL/g (sandy loam). Based on these laboratory results, fenbuconazole is immobile in loam and sandy loam and has slight to low potential for mobility in clay, sand and silty clay loam. Adsorption appears to be associated with the percentage of organic matter present in soil. According to the classification scheme of McCall et al. (1981), fenbuconazole will be slightly mobile in soils containing a low percentage of organic carbon (generally ≤1%) and relatively immobile in soils with higher levels of organic carbon. The results from the desorption phase were not accepted for Canadian regulatory purposes.

An aged-soil leaching study was conducted on the sandy loam soil used in the adsorption/desorption study. Less than 1% of the recovered activity was detected beyond the 0–6 cm segment, 0.2% of the activity was found in the leachate and <1.0% $^{14}CO_2$ evolved during the aging process. Three minor transformation products (RH-99129, RH-99130 and RH-96467) were detected in the aged soil residues, accounting for less than 10% of the total activity. RH-99129 and RH-99130 are diastereomers. The K_{oc} value was calculated to be >3445. Thus, according to the classification scheme of McCall et al. (1981), fenbuconazole has a slight potential for mobility in sandy loam soil. In the adsorption/desorption study, the adsorption K_{oc} value for sandy loam was 9000, for which RH-7592 is classified as immobile according to McCall et al. (1981).

Thus, from the laboratory studies of mobility, fenbuconazole is relatively immobile in soils and would not be expected to leach. Based on the Henry's Law constant and vapour pressure (see Table 1.2.1), fenbuconazole is not expected to volatilize from soils or moist surfaces, including water. The high K_{oc} and K_{om} indicate that fenbuconazole is expected to partition to sediments. Partitioning to sediments was confirmed in the study on biotransformation in aerobic water/sediment.

5.5 Dissipation and Accumulation under Field Conditions

Under terrestrial field conditions, the DT_{50}s of fenbuconazole were calculated by the registrant to be 161 days and 314 days at the Midwest and Northern California field sites,

respectively. These DT_{50}s are in general agreement with those reported in the aerobic soil biotransformation study (285 and 367 days in silty clay loam and sand loam, respectively). Examination of the data by the PMRA indicates that the DT_{50} at the Midwest site was >364 days at 1 of 3 replicate plots and could not be determined at the 2 other plots. Similarly, the PMRA determined that the DT_{50}s at the northern California plots were 198 days at one of the three replicate plots and >364 days at two of the replicate plots. The data indicate that fenbuconazole is persistent under field conditions according to the classification scheme of Goring et al. (1975). Major transformation products were not detected in the field studies, although four minor transformation products (RH-9130, RH-9129, RH-6467 and 1,2,4-triazole) were measured.

Based on the long DT_{50}s, carryover of residues of fenbuconazole and its transformation products will occur if repeated applications are made from season to season. If the compound's use is extended to field crops, these residues may be available for uptake by rotated crops. Residues of some transformation products were infrequently detected below 30 cm; however, there was no general trend for leaching over the 12- to 18-month duration of the field trials. Despite the lack of leaching, the pattern of dissipation of fenbuconazole was not clearly identified in the two sites applicable to Canadian conditions; therefore, the guideline requirements for a terrestrial field dissipation study have not been fulfilled.

There is good agreement between laboratory and field data in the classification of the persistence, lack of leaching and immobility of fenbuconazole in soil. The exact dissipation route of fenbuconazole in soil has not been confirmed between laboratory and field studies.

In a separate field study, the percent interception of fenbuconazole by orchard trees was calculated to be 56% and the DT_{50} on turf was determined to be 6.7 days. It should be noted that this study was not conducted according to any international protocol and good laboratory practices or quality assurance were not provided. Therefore, the results should be interpreted with caution.

Data are not available on the dissipation of fenbuconazole under aquatic field conditions.

5.6 Bioaccumulation

The *n*-octanol–water coefficient for fenbuconazole is 1700 ± 300. Given that the log K_{ow} exceeds 3 (log K_{ow} = 3.22 ± 0.08), there is potential for the compound to bioaccumulate in biological organisms. The PMRA identified the parent compound (fenbuconazole) and RH-9129/RH-9130 (the lactone stereoisomers) as the residues of concern in plants. No residue of concern was identified for animals because stone fruits are not fed to animals.

A laboratory study with rats indicated that fenbuconazole was rapidly absorbed, distributed and excreted primarily via the feces within 24 to 48 hours postdosing. Tissue

distribution and bioaccumulation were minimal. Elimination was biphasic with an initial rapid phase (24–48 hours postdosing) followed by a slower decline (48–96 hours postdosing).

Although three studies on the bioaccumulation in fish were submitted, only two studies were reviewed (see Appendix I for rationale for not reviewing the additional study). Similar results were found for fish, although the elimination period was longer than in rats. Bioconcentration factors for bluegill sunfish were 170×, 50×, and 330× in whole fish, fillets and visceral tissues, respectively, with 95–98% of concentrated residues depurated over a 14-day period. Five transformation products were identified: lactone A (RH-9129), a ketone (RH-6467), two polar stereoisomers and the sulfate conjugate of a benzyl alcohol intermediate in the pathway leading to formation of the lactone and ketone. An unknown transformation product was tentatively identified as the glucorinide conjugate of the proposed benzylic alcohol intermediate.

5.7 Summary of Fate and Behaviour in the Terrestrial Environment

Fenbuconazole undergoes very limited phototransformation on soil with a DT_{50} of 79 days. Therefore, fenbuconazole is not subject to abiotic transformation mechanisms in the terrestrial environment.

Biotransformation is a route of transformation of fenbuconazole in aerobic and anaerobic soils, although this is a slow process in aerobic soils (half-lives of 258 and 367 days for aerobic silty clay loam and sandy loam soils, respectively) and a very slow process is anaerobic soils (half-lives of 451 and 655 days in anaerobic silty clay loam and sandy loam, respectively). Thus, fenbuconazole is classified as persistent in soil under both aerobic and anaerobic conditions. Two major transformation products were detected in aerobic soils (RH-9129 and free triazole). As fenbuconazole is non-volatile, studies on the biotransformation in air are not required.

The mobility of fenbuconazole was reviewed in laboratory studies of adsorption/desorption and aged-soil leaching. The adsorption K_d values for fenbuconazole range from 5.1 to 115 mL/g, while corresponding adsorption K_{oc} values range from 2185 to 9042 mL/g. Fenbuconazole is classified as immobile in loam and sandy loam and has slight to low potential for mobility in clay, sand and silty clay loam. Adsorption appears to be associated with the percentage of organic matter present in soil. Fenbuconazole will be slightly mobile in soils containing a low percentage of organic carbon (generally ≤ 1%) and relatively immobile in soils with higher levels of organic carbon. The results from the desorption phase were not accepted for Canadian regulatory purposes. In an aged-soil leaching study, less than 1% of the recovered activity was detected beyond the 0–6 cm segment, in the leachate or as $^{14}CO_2$. A K_{oc} value was calculated to be greater than 3445, indicating that fenbuconazole has slight potential for mobility in sandy loam soil. In the adsorption/desorption study, the adsorption K_{oc} value for sandy loam was 9000, for which RH-7592 was classified as immobile.

Thus, from the laboratory studies of mobility, fenbuconazole is relatively immobile in soils and would not be expected to leach. Based on the Henry's Law constant and vapour pressure (Table 1.2.1), fenbuconazole is not expected to volatilize from soils or moist surfaces, including water. The high K_{oc} and K_{ow} indicate that fenbuconazole may be expected to partition to sediments. Partitioning to sediments was confirmed in the study on biotransformation in aerobic water/sediment.

Under terrestrial field conditions, the registrant reported DT_{50}s of 161 and 314 days for fenbuconazole at two field sites. These half-lives are in general agreement with those reported in the aerobic soil biotransformation study. Examination of the data by the PMRA indicates that the DT_{50} at the Midwest site was >364 days at 1 of 3 replicate plots and could not be determined at the 2 other plots. Similarly, the PMRA determined that the DT_{50}s at the northern California plots were 198 days at one of the three replicate plots and >364 days at two of the replicate plots. The data indicate that fenbuconazole is persistent under field conditions. Major transformation products were not detected in the field studies, although four minor transformation products (RH-9130, RH-9129, RH-6467 and 1,2,4-triazole) were measured. No leaching was observed; however, based on the reportedly long half-lives, carryover of residues of fenbuconazole and its transformation products will occur if repeated applications are made from season to season. If the compound's use is extended to field crops, these residues may be available for uptake by rotated crops. Although there is good agreement between laboratory and field data in the classification of the persistence, lack of leaching and immobility of fenbuconazole in soil, the exact dissipation route of fenbuconazole in soil has not been confirmed between laboratory and field studies. As the pattern of dissipation of fenbuconazole was not clearly identified, the guideline requirements for a terrestrial field dissipation study have not been fulfilled. However, as the laboratory data support the persistence of fenbuconazole, no terrestrial field study is required at this time. In a separate field study, the percent interception of fenbuconazole by orchard trees was calculated to be 56% and a half-life on turf was determined to be 6.7 days.

Given the *n*-octanol–water coefficient for fenbuconazole of 1700 ± 300 (log K_{ow} = 3.22 ± 0.08), there is potential for the compound to bioaccumulate in biological organisms. Although fenbuconazole accumulated in both rats and fish, the compound was depurated from both organisms with a more rapid elimination in rats than in fish. The transformation products in fish included RH-9129 (lactone), RH-6467 (ketone), two polar stereoisomers and the sulfate conjugate of a benzyl alcohol intermediate in the pathway leading to formation of the lactone and ketone. A third transformation product was tentatively identified as the glucorinide conjugate of the benzylic alcohol intermediate.

5.8 Summary of Fate and Behaviour in the Aquatic Environment

Fenbuconazole may be expected to enter the aquatic environment through direct overspray, spray drift from orchard blast application and/or runoff via adsorption to soil particles.

Fenbuconazole does not undergo hydrolysis or phototransformation in water at environmentally relevant pHs. No major or minor transformation products were formed in either of the studies on the hydrolysis or phototransformation of fenbuconazole in water.

Studies on the biotransformation of fenbuconazole in aerobic water and in anaerobic sediment/water were not submitted because fenbuconazole partitions to sediment and the behaviour in sediment was described in the anaerobic segment of the aerobic water/sediment study. In a study on the biotransformation of fenbuconazole in aerobic water/sediment, the longest dissipation times for water were 4.3 days and 1.2 days in river and pond water, respectively, indicating that fenbuconazole is rapidly removed from water (non-persistent). Although dissipation times for sediment were not presented, the DT_{50}s for the river and pond water/sediment systems exceeded 1000 days. Major transformation products were not detected in the aerobic water/sediment study. Although minor transformation products were formed, aerobic biotransformation in water/sediment is not an important route of transformation of fenbuconazole. The fate of fenbuconazole in aerobic water/sediment systems is partitioning to sediment where it is classified as persistent.

Data are not available on the dissipation of fenbuconazole under aquatic field conditions.

5.9 Expected Environmental Concentrations

The expected environmental concentrations (EEC) of fenbuconazole in environmental compartments of concern were estimated based on calculations made using simple scenarios. These concentrations were used as initial approximations for estimating the potential exposure to wildlife. It was assumed that fenbuconazole was applied at the maximum proposed Canadian label rate of 0.105 kg a.i./ha. The application pattern was based on the tentative application uses supported by the PMRA: 7 applications per season with applications 7 days apart with the exception of a 60-day interval between application numbers 5 and 6. The scenario assumes that the concentrations in the various environmental compartments were obtained immediately following the last of the applications.

5.9.1 Soil

The EEC of fenbuconazole in soil was calculated assuming application to bare soil with a soil bulk density of 1.5 g/cm^3 and a soil depth of 15 cm. Seven applications at the maximum proposed Canadian label rate of 0.105 kg a.i./ha were used in the pattern outlined in Section 5.9. Using the most conservative registrant-reported DT_{50} of 314 days in soil (field dissipation study), the concentration of fenbuconazole in soil immediately following the seventh application is equivalent to a cumulative application of 0.650 kg a.i./ha. Based on the maximum cumulative application rate, the EEC in soil was estimated to be 0.29 mg a.i./kg soil dry weight (dw).

5.9.2 Aquatic Systems

The DT_{50} of 4.3 d from the study on the biotransformation of fenbuconazole in aerobic water/sediment was used to calculate the EEC resulting from direct overspray of fenbuconazole to aquatic systems. Using the application pattern outlined in Section 5.9 (7 applications at the maximum proposed Canadian label rate of 0.105 kg a.i./ha at 7-day and 60-day intervals), the EEC of fenbuconazole in water immediately following the seventh application is the equivalent of a cumulative application of 0.150 kg a.i./ha. Assuming a scenario in which a body of water 30 cm deep is oversprayed with the equivalent of the cumulative application rate, the EEC in water is 0.05 mg a.i./L water. Although this scenario may be unrealistic for ground application, it is useful as a first approximation and is used to compare the EECs in aquatic systems and the no observed effect concentrations (NOECs) from environmental toxicology studies.

Based on the potential use pattern of fenbuconazole in areas where stone fruits are grown, residues of fenbuconazole in potential drinking water sources in these areas (i.e., groundwater and reservoirs) were modelled using the Leaching Estimation and Chemistry Model (LEACHM) for groundwater and the Pesticide Root Zone Model/Exposure Analysis Modelling System (PRZM/EXAMS) for surface water. As the proposed use pattern does not include use in the prairie region, concentrations of fenbuconazole in dugouts were not determined.

Because the modelling results from the Level I screening model failed the human health assessment conducted by the PMRA, a refined analysis was conducted (Level II). The Level II analysis represents a less conservative approach to predicting drinking water concentrations of the active ingredient as it more accurately reflects the use pattern of the chemical. Three scenarios typical of stone fruit growing regions were used in the water modelling: an apple growing region in British Columbia; a grape growing region in Niagara, Ontario; and an apple growing region in Nova Scotia. Because, in general, the most suitable soils for stone fruit production in Canada are sandy loam soils, the Level II assessment used input parameters specific to sandy loam soil, where applicable.

The most conservative estimates of the EECs in drinking water sources were 2.2 μg a.i./L and 0.25 μg a.i./L for acute and chronic exposures, respectively. These values were provided for the human health assessment. As a Level II drinking water assessment was conducted, any further use expansion beyond stone fruit growing regions (e.g., Okanagan Valley, British Columbia or the Niagara Region, Ontario) will require a re-evaluation of drinking water concentrations for two reasons: concentrations in dugouts were not examined and the use of fenbuconazole may be expanded to new crops for which drinking water scenarios were not modelled at Level II.

5.9.3 Vegetation and Other Food Sources

Data were not provided on concentrations of fenbuconazole on foliar crops immediately after application. In the absence of these data, concentrations of fenbuconazole on vegetation and insects resulting from direct overspray were estimated using a nomogram developed by the USEPA from the data of Hoerger and Kenaga (1972) and Kenaga (1973), for use in ecological risk assessment (Urban and Cook 1986). EECs were determined for two scenarios:

1) no transformation between first and last (seventh) application and no interception of airblast spray by orchard trees (Table 5.9.3a)
2) dissipation from turf using a DT_{50} of 6.7 days and 56% interception of airblast spray (from Batra 1995, DACO 8.2.3.6). This refined scenario was applied to all vegetative matter in the diets of wild birds and mammals (Table 5.9.3b).

A fresh weight to dry weight conversion was calculated for both scenarios.

Table 5.9.3a Maximum EEC in Vegetation and Insects after a Direct Overspray Assuming No Transformation and No Interception of Airblast Spray by Orchard Trees

Matrix	EEC (mg a.i./kg fw)[a]	Fresh/Dry Weight Ratios	EEC (mg a.i./kg dw)
Short range grass	157	3.3[b]	519
Leaves and leafy crops	82.3	11[b]	906
Long grass	72.0	4.4[b]	317
Forage crops	88.2	5.4[b]	476
Small insects	38.2	3.8[c]	145
Pods with seeds	7.86	3.9[c]	30.7
Large insects	6.54	3.8[c]	24.9
Grain and seeds	6.54	3.8[c]	24.9
Fruit	9.85	7.6[c]	74.9

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)
[b] Fresh/dry weight ratios from Harris (1975)
[c] Fresh/dry weight ratios from Spector (1956)

Table 5.9.3b Maximum EEC in Vegetation after a Direct Overspray Assuming Dissipation on Vegetation and Interception of Airblast Spray by Orchard Trees

Matrix	EEC (mg a.i./kg fw)[a]	Fresh/Dry Weight ratios	EEC (mg a.i./kg dw)
Short range grass	18.6	3.3[b]	61
Leaves and leafy crops	9.74	11[b]	107
Long grass	8.5	4.4[b]	38
Forage crops	10.4	5.4[b]	56
Pods with seeds	0.93	3.9[c]	3.6
Grain and seeds	0.77	3.8[c]	2.9
Fruit	1.17	7.6[c]	8.9

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)
[b] Fresh/dry weight ratios from Harris (1975)
[c] Fresh/dry weight ratios from Spector (1956)

Wild birds and mammals could be exposed to residues of fenbuconazole as a result of the consumption of sprayed vegetation and/or contaminated prey. The EECs of fenbuconazole in the diets of bobwhite quail (*Colinus virginianus*), mallard ducks (*Anas platyrhynchos*), rats, mice and rabbits were calculated for the two scenarios presented in Table 5.9.3a and Table 5.9.3b. The calculations of the EECs used in the risk assessment for wild birds and mammals are outlined below and presented in Table 5.9.4.

Wild Bird Scenario 1 (no transformation and no interception assumed):
The EECs of fenbuconazole in the diets of bobwhite quail (*Colinus virginianus*) and mallard duck (*Anas platyrhynchos*) were calculated based on the maximum proposed application rate of 0.735 kg a.i./ha (Table 5.9.4). The diet of bobwhite quail consists of approximately 55% grain, 30% small insects and 15% forage crops. The EECs of fenbuconazole on these items were calculated to be 13.7, 43.6 and 71.4 mg a.i./kg dry weight of diet, respectively, based on the maximum application rate of 0.735 kg a.i./ha. Therefore, the EEC of fenbuconazole in the diet of the bobwhite quail is 129 mg a.i./kg dw. For mallard ducks, the diet consists of approximately 70% grain and 30% arthropods. The EECs of fenbuconazole on these items were calculated to be 17.4 and 7.5 mg a.i./kg dw of diet, respectively, based on the maximum application rate of 0.735 kg a.i./ha. Therefore, the EEC of fenbuconazole in the diet of the mallard duck is 25 mg a.i./kg dw.

Wild Bird Scenario 2 (assumes transformation using DT_{50} for turf and 56% interception):
The EECs in diets of bobwhite quail and mallard duck decrease significantly when transformation on vegetation and interception of the airblast spray by orchard trees are taken into account. For bobwhite quail, the EEC decreases from 129 mg a.i./kg dw to 53.5 mg a.i./kg dw. For mallard duck, the EEC in the diet is reduced from 25 mg a.i./kg dw to 9.5 mg a.i./kg dw. The refined EECs from Wild Bird Scenario 2 are approximately 59% and 62% less than those from the unrefined Wild Bird Scenario 1 for the bobwhite quail and mallard duck, respectively.

Wild Mammal Scenario 1 (no transformation and no interception assumed):
The rat diet consists of approximately 70% short grass, 20% grain/seeds and 10% large insects. The EECs of fenbuconazole on these items were calculated to be 363, 5.0 and 2.5 mg a.i./kg dw, respectively. Therefore, the EEC in the diet of the rat is approximately 371 mg a.i./kg dw. For mice, the diet consists of approximately 50% grain/seeds, 25% short grass and 25% leaves/leafy crops for which the EECs were calculated as 12.4, 130 and 226 mg a.i./kg dw, respectively. Therefore, the EEC in the diet of the mouse is approximately 369 mg a.i./kg dw. For rabbits, the diet consists of approximately 25% of each of short grass, leaves/leafy crops, long grass and forage crops. The EECs on these items were calculated to be 130, 226, 79.2 and 119 mg a.i./kg dw, respectively. Therefore, the EEC in the diet of the rabbit is approximately 554 mg a.i./kg dw.

Wild Mammal Scenario 2 (assumes transformation using DT_{50} for turf and 56% interception):
For the three mammalian species, the EECs in diets decrease significantly when transformation on vegetation and interception of the airblast spray by orchard trees are taken into account. For rats, the EEC decreases from 371 mg a.i./kg dw to 50 mg a.i./kg dw. For mice, the EEC in the diet is reduced from 369 mg a.i./kg dw to 54 mg a.i./kg dw. For rabbits, the EEC is reduced from 554 mg a.i./kg dw to 170 mg a.i./kg dw. The refined EECs from Wild Mammal Scenario 2 are approximately 87%, 85% and 69% less than those from the unrefined Wild Mammal Scenario 1 for the rat, mouse and rabbit, respectively.

Table 5.9.4 Maximum EEC in Diets of Birds and Mammals with and Without the Assumption of Transformation on Vegetation and Interception of Airblast Spray by Orchard Trees

Organism	Matrix	Maximum EEC (mg a.i./kg dw diet)	
		Assuming No Transformation and No Interception	Assuming Transformation and Interception
Bobwhite quail	30% small insects 15% forage crops 55% grain	129	53.5
Mallard duck	30% large insects 70% grain	25	9.5
Rat	70% short grass 20% grain/seeds 10% large insects	371	50
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	369	54
Rabbit	25% short grass 25% leaves and leafy crops 25% long grass 25% forage crops	554	170

6.0 Effects on Non-target Species

6.1 Effects on Terrestrial Organisms

The toxicity of fenbuconazole was studied on earthworms, honeybees and beneficial arthropod species. As fenbuconazole had no significant effect on earthworm survival at any concentration tested, fenbuconazole is considered to be non-toxic to earthworms up to a concentration of 98 mg a.i./kg dw. There were no compound-related toxicity effects in an acute contact study with honeybees and fenbuconazole is classified as relatively

non-toxic to honeybees. The LD_{50} of >292 μg a.i./bee is equivalent to an application rate of >327 kg a.i./ha, which exceeds the proposed single application rate of 0.105 kg a.i./ha by more than 3000 times. Fenbuconazole had no significant effects on the predatory and parasitic arthropods tested and is considered harmless at the maximum application rate for Canada.

Studies on the acute oral toxicity, acute dietary toxicity and reproductive toxicity to birds were reviewed. Although compound-related effects were observed in all studies, fenbuconazole is classified as practically non-toxic to bobwhite quail on an acute oral basis, based on the LD_{50} of >2150 mg a.i./kg bw. The single-dose acute oral NOEL was 1470 mg a.i./kg bw. In addition to four mortalities observed in the highest dose group (out of 10 birds), a variety of sublethal effects were observed. In the acute dietary studies, fenbuconazole would be classified as slightly toxic to bobwhite quail and mallard duck on an acute dietary basis based on the lethal concentrations 50% (LC_{50}s) of 4954 and 2013 mg a.i./kg dw of diet, respectively. The NOEC was 312 mg a.i./kg diet for both species, although various sublethal effects were noted in the three highest test concentrations and physiological changes were observed on gross necropsy in some birds. In the reproduction toxicity studies, the NOEC of fenbuconazole to both bobwhite quail and mallard duck was 150 mg a.i./kg dw. No overt sign of toxicity was noted; however, significant reductions in growth (body-weight gain) and biologically significant decreases in egg production and reduced hatchability were found at 600 mg a.i./kg dw. A toxicant-mediated effect on egg shell thickness was identified for bobwhite quail; therefore, there are toxicant-mediated effects on reproduction in avian species.

Supplemental herbicide screening reports indicate that fenbuconazole does not cause symptoms of injury (phytotoxic effects) to the 11 crops tested at application rates of 75, 150 and 750 g a.i./ha; however, insufficient information was provided for a full scientific review. The most sensitive monocot and dicot species could not be determined from the submitted information. The effect concentration 25% (EC_{25}) and the effect concentration 50% (EC_{50}) for both monocots and dicots was >750 g a.i./ha. The NOEC was 750 g a.i./ha, which exceeds the maximum proposed seasonal application rate of 735 g a.i./ha. Additional studies on the toxicity of fenbuconazole to terrestrial vascular plants were not submitted.

6.2 Effects on Aquatic Organisms

Based on an acute toxicity with *Daphnia magna*, fenbuconazole is classified as moderately toxic to *Daphnia magna*. In a chronic study with *Daphnia magna*, fenbuconazole had an effect on the reproduction at concentrations greater than 0.078 mg a.i./L. In a subchronic study with midge larvae (*Chironomus riparius*), effects on survival and emergence were observed. Given the high partitioning of this product to sediments, and its relatively high toxicity, additional data on toxicity to benthic organisms will be required if the use pattern is expanded beyond what is currently proposed for stone fruit.

Fenbuconazole was found to be acutely moderately toxic to rainbow trout and highly toxic to bluegill sunfish. Sublethal effects were also observed in both species. In an early life-stage test, fenbuconazole did not significantly affect hatching success or larval survival of early life stages of fathead minnows; however, standard length was significantly reduced at the highest test concentration and wet weight was significantly reduced at the two highest test concentrations (0.16 and 0.33 mg a.i./L). Other sublethal effects were observed. In a full life-cycle toxicity study with fathead minnow, the most sensitive endpoint identified was the time to first spawn, with a NOEC of 0.027 mg a.i./L. Other measurement endpoints were also affected at higher concentrations, including number of eggs produced, survival of parents and offspring as well as numbers of eggs per spawn.

In fish, results on the bioaccumulation of fenbuconazole were found to be similar to those in rats, although the elimination period was longer in fish. Bioconcentration factors for bluegill sunfish were 170×, 50× and 330× in whole fish, fillets and visceral tissues, respectively, with 95–98% of concentrated residues being depurated over a 14-day period. Five transformation products were identified: lactone A (RH-9129), a ketone (RH-6467), two polar stereoisomers and the sulfate conjugate of a benzyl alcohol intermediate in the pathway leading to formation of the lactone and ketone. Further transformation products were tentatively identified as the glucorinide conjugate of the benzylic alcohol intermediate.

Studies on the acute toxicity to two species of freshwater green algae, one diatom and one blue-green algae were reviewed. The most sensitive algal species was *Selenastrum capricornutum* Printz, with a NOEC of 0.270 mg a.i./L and the percent growth inhibition in the treated algal culture as compared to the control ranged from 0 to 100%. Abnormalities were noted in the higher concentrations tested including bloating and irregularly shaped algal cells.

Studies on the acute toxicity to a marine crustacean and toxicity to mollusk embryo larvae were reviewed. A study of the acute toxicity of fenbuconazole to *Mysidopsis bahia* determined that fenbuconazole is highly toxic to mysid shrimp. Significant differences in shell deposition were observed for the Eastern Oyster exposed to fenbuconazole. The NOEC and the lowest observable effect concentration (LOEC) were 0.53 and 0.69 mg a.i./L, respectively, with a 32% decrease in shell deposition at the LOEC level. As an EC_{50} was not determined, fenbuconazole is classified as highly toxic to the Eastern Oyster based on the LOEC. In a 96-h acute toxicity study on sheepshead minnow, *Cyprinodon variegatus*, the LC_{50} and NOEC were 1.8 and 0.89 mg a.i./L, respectively; thus, fenbuconazole is classified as moderately toxic to sheepshead minnow. Sublethal effects were also observed. Data were not submitted on the toxicity to marine algae.

6.3 Effects on Biological Methods of Sewage Treatment

As data are not required, data were not submitted.

6.4 Risk Characterization

6.4.1 Environmental Behaviour

As summarized in sections 5.7 and 5.8, fenbuconazole is persistent in soil and sediment. Therefore, in addition to acute exposure there is potential for prolonged exposure of soil- and sediment-dwelling organisms to residues of fenbuconazole. Further exposure of terrestrial organisms can be expected from the consumption of contaminated vegetation. Results from laboratory and field studies as well as groundwater modelling (Section 5.9.2) indicate that fenbuconazole is not likely to leach into groundwater. However, fenbuconazole may be expected to enter the aquatic environment through direct overspray, spray drift from orchard blast application and/or runoff via sorption to soil particles. Therefore, there is potential for exposure of fenbuconazole to non-target terrestrial and aquatic organisms. Based on the physicochemical properties of fenbuconazole, volatilization is not an expected route of exposure of non-target organisms.

In order to minimize entry into the environment, a summary of storage, disposal and decontamination procedures for the active ingredient is required. The instructions for storage, disposal and decontamination are consistent with avoiding entry of fenbuconazole into the environment.

6.4.2 Terrestrial Organisms

The submitted toxicity studies were conducted using the parent compound. Data were not submitted on the toxicity of transformation products of fenbuconazole to terrestrial organisms. Therefore, the terrestrial risk assessment is for the parent compound, fenbuconazole.

The degree of risk to terrestrial (and aquatic) organisms was classified according to the following index:

Margin of Safety (MOS)	Risk Qualifier
≥10	Negligible risk
1 to <10	Low risk
0.1 to <1	Moderate risk
0.01 to <0.1	High risk
0.001 to <0.01	Very high risk
<0.001	Extremely high risk

6.4.2.1 Non-target Terrestrial Invertebrates

6.4.2.1.1 Earthworms

One scientifically valid and acceptable toxicity study with earthworms was submitted. The NOEC was 98 mg a.i./kg soil. The EEC of fenbuconazole in soil (0.29 mg a.i./kg soil) is below the NOEC. The MOS is 340; therefore, fenbuconazole poses a negligible risk to earthworms at the proposed application rate (Appendix IV, Table 5).

6.4.2.1.2 Bees

One scientifically valid and acceptable acute contact toxicity study with honeybees was submitted. According to the classification scheme of Atkins et al. (1981), fenbuconazole is relatively non-toxic to bees.

The LD_{50} for honeybees was >292 μg a.i./bee, which is equivalent to >327 kg a.i./ha. The maximum seasonal application rate of 0.735 kg a.i./ha is lower than the LD_{50}. As the MOS is 445, fenbuconazole poses a negligible risk to honeybees at the proposed application rate (Appendix IV, Table 5).

6.4.2.1.3 Predators and Parasites

Fenbuconazole had no significant effects on the predatory and parasitic arthropods tested, i.e., the parasitic wasp (*Aphidius rhoplosiphi*), the predatory mite (*Typhlodromus pyri*), the foliage-dwelling predators (*Chrysoperla carnea* and *Coccinella septempunctata*) and the ground-dwelling predator (*Poecilus cupreus*). Therefore, fenbuconazole is considered harmless to these species at the maximum application rate for Canada (Appendix IV, Table 5).

6.4.2.2 Birds

Wild birds, such as bobwhite quail (*Colinus virginianus*) and mallard duck (*Anas platyrhynchos*), could be exposed to residues of fenbuconazole as a result of the consumption of sprayed vegetation and/or contaminated prey. Based on Table 5.9.4 and assuming no transformation and no interception of orchard blast spray (Wild Bird Scenario 1, see Section 5.9.3), the EECs of fenbuconazole in the diets of the bobwhite quail and mallard duck are 129 and 25 mg a.i./kg dw, respectively. When transformation on vegetation and interception by trees are taken into account (Wild Bird Scenario 2), these EECs decrease to 53.5 and 9.5 mg a.i./kg dw, respectively. Individual risk assessments were carried out for acute oral exposure to bobwhite quail, acute dietary exposure to bobwhite quail and mallard duck and chronic exposure for reproductive effects with both avian species.

One acceptable toxicity study was submitted on the acute oral exposure of wild birds to fenbuconazole. In an acute oral study with bobwhite quail, the LD_{50} was >2150 mg a.i./kg bw, while the NOEL was 1470 mg a.i./kg bw. The average body weight per individual (BWI) of the control group in the study was 204 g and the daily individual (ind) food consumption (FC) was 0.015 kg dw. Therefore, the daily intakes of fenbuconazole (DI = FC × EEC) are 1.94 and 0.80 mg a.i./ind/d under Wild Bird Scenarios 1 and 2, respectively. Expressed on a per individual basis, the $LD_{50\,(ind)}$ and $NOEL_{(ind)}$ were 439 and 300 mg a.i./ind, respectively. Based on the predicted daily intake of the active ingredient and the $LD_{50\,(ind)}$, the number of days of intake of fenbuconazole by a bobwhite quail in the wild to attain a dose equivalent to that administered by gavage that killed 50% of the individuals in the laboratory population is 227 and 547 days under Wild Bird Scenarios 1 and 2, respectively. Similarly, based on the predicted daily intake and the $NOEL_{(ind)}$, the maximum number of days of intake of fenbuconazole by a wild bobwhite quail, to attain a dose equivalent to that administered by gavage that had no observable effect on the laboratory population, is 155 and 374 days, under Wild Bird Scenarios 1 and 2, respectively. These values indicate that the application of fenbuconazole at the maximum proposed label rate poses a negligible risk to wild bird populations, such as the bobwhite quail, that are acutely exposed to fenbuconazole (Appendix IV, Table 5).

The LD_{50}s from separate acute dietary studies with bobwhite quail and mallard duck were 4954 mg a.i./kg diet and 2013 mg a.i./kg diet, respectively. According to the USEPA classification scheme, fenbuconazole is considered slightly toxic when birds are acutely exposed. The NOECs were 625 and 312 mg a.i./kg dw diet for bobwhite quail and mallard duck, respectively. Under Wild Bird Scenario 1, the EECs in the diet of the bobwhite quail and the mallard duck are expected to be 129 and 25 mg a.i./kg dw, respectively. Thus, the MOS for bobwhite quail and mallard duck are 4.8 and 13, respectively. Therefore, under Wild Bird Scenario 1, fenbuconazole is considered to pose a low dietary risk to bobwhite quail and a negligible dietary risk to mallard ducks at the proposed maximum application rate (Appendix IV, Table 5). Under the refined Wild Bird Scenario 2, which takes into account transformation on vegetation and interception by orchard trees, the EECs in the diet of the bobwhite quail and the mallard duck are expected to be 53.5 and 9.5 mg a.i./kg dw, respectively. Thus, the MOS for bobwhite quail and mallard duck are 12 and 33, respectively. Therefore, according to Wild Bird Scenario 2, fenbuconazole poses a negligible dietary risk to wild birds at the proposed maximum application rate (Appendix IV, Table 5).

Two chronic studies were submitted that examined reproductive effects in bobwhite quail and mallard duck. For both species, the NOEL and the lowest observed adverse effect level (LOAEL) were 150 and 600 mg a.i./kg diet, respectively. For bobwhite quail, under Wild Bird Scenario 1, the NOEL slightly exceeds the EEC in the diet of 129 mg a.i./kg diet. This results in a MOS of 1.2, indicating a low risk of reproductive effects in bobwhite quail. Consequently, a refined dietary risk assessment was conducted for bobwhite quail using the EEC of 53.5 mg a.i./kg diet (Wild Bird Scenario 2). The refined scenario for bobwhite quail resulted in a MOS of 2.8, which is interpreted as a low risk of reproductive

effects. For mallard ducks, the NOEL also exceeds the EECs of 25 and 9.5 mg a.i./kg diet from Wild Bird Scenarios 1 and 2, respectively. The resultant MOS are 6.0 and 16 for Wild Bird Scenarios 1 and 2, respectively (Appendix IV, Table 5). The MOS for Wild Bird Scenario 2 indicates a negligible risk of reproductive effects occurring in mallard duck following long-term dietary exposure to fenbuconazole.

6.4.2.3 Wild Mammals

Wild mammals such as rats and mice could be exposed to residues of fenbuconazole as a result of the consumption of sprayed vegetation and/or contaminated prey. From Table 5.9.4, assuming no transformation and no interception of orchard blast spray (Wild Mammal Scenario 1, see Section 5.9.3), the EECs of fenbuconazole in the diets of rats, mice and rabbits are 371, 369, and 554 mg a.i./kg dw, respectively. When transformation on vegetation and interception by trees are taken into account (Wild Mammal Scenario 2, see Section 5.9.3), these EECs decrease to 50, 54 and 170 mg a.i./kg dw, respectively.

For rats, BWIs of 0.192 and 0.157 kg and FCs of 0.028 and 0.020 kg dw per individual rat were used for males and females, respectively. Therefore, the daily intakes (DI = FC × EEC) of fenbuconazole are 10 and 7.4 mg a.i./ind/d for males and females, respectively, under Wild Mammal Scenario 1, and 1.4 and 1.0 mg a.i./ind/d for males and females, respectively, under Wild Mammal Scenario 2. Two acute oral toxicity studies were reviewed by the Health Evaluation Division: one for the active ingredient and one for the formulated end-use product. The LD_{50}s in these studies were 5000 and 4000 mg a.i./kg bw for the active and end-use product, respectively. Expressed on a per individual basis, the $LD_{50\,(ind)}$s (LD_{50} × BWI) are 960 and 785 mg a.i./ind for males and females, respectively, in the active ingredient study and 768 and 628 mg a.i./ind for males and females, respectively, in the end-use product study. As NOELs were not available for either study, one-tenth of the LD_{50} was used as the NOEL. The calculated NOELs are, therefore, 500 and 400 mg a.i./kg bw and the $NOEL_{(ind)}$s (NOEL × BWI) are 96.0 and 78.5 mg a.i./ind for males and females, respectively, in the active ingredient study, and 76.8 and 62.8 mg a.i./ind for males and females, respectively, in the end-use product study.

Using the data from the oral toxicity study with the active ingredient, the daily intakes from Wild Mammal Scenarios 1 and 2, and the LD_{50} of individual rats, it would take more than 92 and 106 days of continuous feeding ($LD_{50\,(ind)}$ ÷ DI) under Wild Mammal Scenario 1, and more than 686 and 785 days of continuous feeding under Wild Mammal Scenario 2, for wild male and female rats, respectively, to attain a dose equivalent to that administered by gavage in the laboratory that killed 50% of the laboratory population. Based on the study with the end-use product, it would take more than 74 and 85 days of continuous feeding under Wild Mammal Scenario 1, and more than 549 and 628 days of continuous feeding under Wild Mammal Scenario 2, for wild male and female rats, respectively, to attain a dose equivalent to that administered by gavage in the laboratory that killed 50% of the laboratory population.

As the NOELs used in the risk assessment are one-tenth of the LD_{50}s, the maximum number of days of intake of fenbuconazole by a wild rat to attain a dose equivalent to that administered by gavage in the laboratory that had no observable effect on the laboratory population is also one-tenth of the number of days of intake to accumulate a dose equivalent to that administered by gavage that killed 50% of the laboratory population. Thus, from the active ingredient study, the maximum number of days of intake to reach the laboratory dosage that had no observable effect is 9.2 and 11 days for male and female rats, respectively, under Wild Mammal Scenario 1, and 69 and 79 days for male and female rats, respectively, under Wild Mammal Scenario 2. Similarly, from the end-use product study, the maximum number of days of intake to reach the laboratory dosage that had no observable effect is 7.4 and 8.5 days for male and female rats, respectively, under Wild Mammal Scenario 1, and 55 and 63 days for male and female rats, respectively, under Wild Mammal Scenario 2. The results from the most sensitive rat (males in end-use product study) are presented in Appendix IV, Table 5.

For mice, one acute oral toxicity study was reviewed. BWI of 0.031 and 0.023 kg were used for males and females, respectively. Using a mean FC rate of 0.006 kg dw per individual mouse per day, the daily intake (DI = FC × EEC) of fenbuconazole is 2.2 or 0.3 mg a.i./ind/d for Wild Mammal Scenario 1 and the refined Wild Mammal Scenario 2, respectively. The LD_{50} was 5000 mg a.i./kg bw; when expressed on a per individual basis, the $LD_{50\,(ind)}$ (LD_{50} × BWI) is 155 and 115 mg a.i./ind for males and females, respectively. Based on the daily intakes and the LD_{50} of individual mice, it would take more than 70 and 52 days of continuous feeding ($LD_{50\,(ind)}$ ÷ DI) under Wild Mammal Scenario 1, or 478 and 355 days under Wild Mammal Scenario 2 for wild male and female mice, respectively, to attain a dose equivalent to that administered by gavage in the laboratory that killed 50% of the laboratory population. As for the rat studies, since the NOEL was not available, one-tenth of the LD_{50} was used in the risk assessment of the acute toxicity to mice. The calculated NOEL is, therefore, 500 mg a.i./kg bw and the $NOELs_{(ind)}$ (NOEL × BWI) are 15.5 and 11.5 mg a.i./ind for males and females, respectively. Therefore, the maximum numbers of days of intake of fenbuconazole by a wild mouse to attain a dose equivalent to that administered by gavage in the laboratory with no observable effect on the laboratory population are 7.0 and 5.2 days under Wild Mammal Scenario 1, and 48 and 36 days under Wild Mammal Scenario 2, for males and females, respectively. The results from the most sensitive mouse (females) are presented in Appendix IV, Table 5.

Based on the above assessments, application of fenbuconazole at the maximum proposed label rate poses a negligible acute risk to populations of wild mammals that are exposed to fenbuconazole on vegetation in their diet.

In the dietary studies with male and female rats, the most sensitive NOEC was 20 mg a.i./kg dw (3-month study, male rats). Using an EEC of 371 mg a.i./kg dw (Wild Mammal Scenario 1), the MOS is 0.05, which indicates a high risk to rats. A refined assessment was performed using the EEC of 50 mg a.i./kg dw from Wild Mammal Scenario 2. In the refined scenario, which takes into account transformation and interception of the air blast spray by orchard trees, the MOS is 0.40, indicating moderate risk to rats (Appendix IV, Table 5).

A similar assessment was performed for the dietary studies with male and female mice. The most sensitive NOEC was 10 mg a.i./kg dw for both male and female mice (78-week study). Using an EEC of 369 mg a.i./kg dw (Wild Mammal Scenario 1), the MOS is 0.027, which indicates a high risk to mice. A refined assessment was performed using the EEC of 54 mg a.i./kg dw from Wild Mammal Scenario 2. In the refined scenario, the MOS is 0.19, indicating moderate risk to mice (Appendix IV, Table 5).

Based on the reproductive studies with rats, the most sensitive NOEC was 80 mg a.i./kg dw (for both male and female systemic toxicity and female reproductive toxicity). Using an EEC of 371 mg a.i./kg dw (Wild Mammal Scenario 1), the MOS is 0.22, which indicates a moderate reproductive risk to rats. A refined assessment using the EEC of 50 mg a.i./kg dw from Wild Mammal Scenario 2 was performed. From the refined scenario, the MOS is 1.6, which indicates a low reproductive risk to rats (Appendix IV, Table 5).

Based on the studies with rats and mice, fenbuconazole may pose dietary and reproductive risks to mammals in the wild.

6.4.2.4 Non-target Terrestrial Plants

Three herbicidal screening studies were submitted on the phytotoxicity of fenbuconazole to several species of terrestrial plants. No effect was observed in the Tier I testing at a rate of 750 g a.i./ha. As this exceeds the maximum cumulative application rate of 735 g a.i./ha, the risks to terrestrial vascular plants are expected to be negligible.

6.4.2.5 Summary of Risk to Terrestrial Organisms

Risks to avian and mammalian species were identified following an assessment of the environmental safety associated with the use of fenbuconazole. The most sensitive endpoints are reported in Appendix IV, Table 5. Using the proposed pattern of seven applications per year at a maximum rate of 0.105 kg a.i./ha and a refined risk assessment, fenbuconazole poses a low reproductive risk to upland game birds and wild mammals and a moderate dietary risk to wild mammals. It should be noted that the risk assessments for wild birds and mammals took into account both a reduced amount of fenbuconazole reaching the ground due to interception by orchard trees and transformation on the vegetation consumed by the birds and mammals (e.g., grasses,

leaves, leafy crops, forage crops, grains, seeds and fruit). Thus, the dietary and reproductive risks may be greater if these two factors are not taken into account. These dietary and reproductive risks are attributed to the systemic and reproductive toxicity of the parent compound to birds and mammals.

Negligible acute risk is posed to earthworms, bees, wild birds and wild mammals. Fenbuconazole is considered harmless to beneficial predatory and parasitic arthropods at the maximum application rate for Canada. The risks to terrestrial vascular plants are expected to be negligible. As fenbuconazole is persistent in soil, natural soil fungi and their processes on decomposition may be affected; however, the absence of data means that the degree to which fungal processes may be affected cannot be assessed. Furthermore, the risks to terrestrial organisms resulting from exposure to major transformation products of fenbuconazole are unknown.

6.4.3 Aquatic Organisms

As for terrestrial organisms, data were not submitted on the toxicity of transformation products of fenbuconazole to aquatic organisms. Therefore, the aquatic risk assessment is for the parent compound, fenbuconazole. The degree of risk to aquatic organisms was classified according to the classification scheme identified in Section 6.4.2.

6.4.3.1 Non-target Freshwater Invertebrates

One accepted study was submitted on the acute toxicity of fenbuconazole to *Daphnia magna*. The 48-h EC_{50} was 2.3 mg a.i./L. Therefore, according to the USEPA classification scheme, fenbuconazole is classified as moderately toxic to daphids. The EEC of fenbuconazole in water (0.05 mg a.i./L) is below the 48-h NOEC of 0.78 mg a.i./L from the acute study. The MOS is 16; therefore, fenbuconazole poses a negligible acute risk to pelagic freshwater invertebrates at the proposed application rate (Appendix IV, Table 6). It should be noted, however, that this result cannot be generalized to all freshwater invertebrates as fenbuconazole partitions to sediment where it may accumulate.

Although a study of the subchronic toxicity of fenbuconazole to *Chrironomus riparius* was reviewed, at the present time, the toxicity to benthic species cannot be accurately assessed as current risk assessment methods do not allow a determination of the EECs in sediment and pore water.

One valid study was submitted to illustrate the chronic toxicity of fenbuconazole to *Daphnia magna*. In a chronic life cycle toxicity test, 21-d NOEC and LOEC for number of young per adult and adult growth was 0.078 mg a.i./L.

6.4.3.2 Non-target Marine Invertebrates

One acceptable study was submitted on the acute toxicity of fenbuconazole to *Mysidopsis bahia*, a pelagic marine crustacean. The 96-h LC_{50} was 0.63 mg a.i./L. Therefore, according to the USEPA classification scheme, fenbuconazole is classified as highly toxic to mysids. The EEC of fenbuconazole in water (0.05 mg a.i./L) is below the 96-h NOEC of 0.16 mg a.i./L. The MOS is 3.2; therefore, fenbuconazole poses a low risk to mysids at the proposed application rate (Appendix IV, Table 6).

A study on the acute toxicity of fenbuconazole to the Eastern Oyster, *Crassostrea virginica*, was accepted. An EC_{50} was not determined. Based on the 96-h LOEC of 0.69 mg a.i./L, fenbuconazole is classified as highly toxic to this marine mollusk according to the USEPA classification scheme. The EEC of fenbuconazole in water (0.05 mg a.i./L) is below the 96-h NOEC of 0.53 mg a.i./L. The MOS is 11; therefore, fenbuconazole poses a negligible acute risk to *C. virginica* at the proposed application rate (Appendix IV, Table 6).

As for freshwater organisms, the results for mysids and mollusks cannot be generalized to all marine invertebrates as fenbuconazole partitions to sediment where it may accumulate and benthic species may be exposed.

6.4.3.3 Fish

Freshwater

Two acceptable studies were submitted on the acute toxicity of fenbuconazole to freshwater fish. For coldwater fish (*Onchorynchus mykiss*, rainbow trout), the 96-h LC_{50} was 1.4 mg a.i./L. Therefore, according to the USEPA classification scheme, fenbuconazole is classified as moderately toxic to coldwater fish. The EEC of fenbuconazole in water (0.05 mg a.i./L) is below the 96-h NOEC of 0.7 mg a.i./L for rainbow trout. The MOS is 14; therefore, fenbuconazole poses a negligible risk to coldwater fish at the proposed application rate (Appendix IV, Table 6).

For warmwater fish (*Lepomis macrochirus*, bluegill sunfish), the 96-h LC_{50} was 0.68 mg a.i./L. Therefore, according to the USEPA classification scheme, fenbuconazole is classified as highly toxic to warmwater fish. The EEC of fenbuconazole in water (0.05 mg a.i./L) is below the 96-h NOEC of 0.42 mg a.i./L for bluegill sunfish resulting in a MOS of 8.4. Therefore, fenbuconazole poses a low risk to warmwater fish at the proposed application rate (Appendix IV, Table 6).

Two early life-stage toxicity tests with fathead minnow (*Pimephles promelas*) were submitted but only one study was found to be acceptable. In the accepted study, various endpoints were affected including wet weight, standard length, spinal curvature and erratic swimming behaviour. The NOEC for the most sensitive endpoint (wet weight at 30 days posthatch) was 0.082 mg a.i./L.

One whole life-cycle toxicity study with fathead minnow (*Pimephles promelas*) was submitted and accepted. In this study, various endpoints were affected including time to first spawn, number of eggs produced, survival of parents and offspring as well as number of eggs per spawn. The NOEC for the most sensitive endpoint (time to first spawn) was 0.027 mg a.i./L.

The EEC of fenbuconazole in water (0.05 mg a.i./L) is less than the early life-stage NOEC of 0.082 mg a.i./L resulting in a MOS of 1.6. Therefore, fenbuconazole may pose a low risk to early life stages of freshwater fish at the proposed application rate (Appendix IV, Table 6). A study of the bioconcentration of fenbuconazole in fish indicates fenbuconazole may accumulate in tissues (BCFs of 330, 170, and 50 in viscera, whole fish and fillets, respectively).

Marine/Estuarine

One acceptable study on the toxicity to marine/estuarine fish (*Cyprinodon variegatus*, sheepshead minnow) was submitted. The 96-h LC_{50} was 1.8 mg a.i./L. Therefore, according to the USEPA classification scheme, fenbuconazole is classified as moderately toxic to marine/estuarine fish. The EEC of fenbuconazole in water (0.05 mg a.i./L) is below the 96-h NOEC of 0.89 mg a.i./L for sheepshead minnow, resulting in a MOS of 18. Therefore, fenbuconazole poses a negligible risk to marine/estuarine fish at the proposed application rate (Appendix IV, Table 6).

6.4.3.4 Algae

Freshwater

Three studies on the phytotoxicity of fenbuconazole to freshwater green alga (*Scenedesmus subspicatus* and *Selenastrum capricornutum*) were submitted, of which two were acceptable for review—one study for each species. One study on the toxicity to a diatom (*Navicula pelliculosa*) and one study on the toxicity to blue-green algae (cyanophyta, *Anabaena flos-aquae*) were also reviewed.

The most sensitive species was *S. capricornutum*. The EEC of fenbuconazole in water (0.05 mg a.i./L) is below the 120-h NOEC of 0.27 mg a.i./L. This results in a MOS of 5.4. Therefore, fenbuconazole poses a low risk to freshwater algae at the proposed application rate (Appendix IV, Table 6).

Marine

As data were not submitted on the toxicity to marine species of algae, the risk to marine algae cannot be assessed at this time.

6.4.3.5 Aquatic Vascular Plants

As the toxicity study with the aquatic vascular plant *Lemna gibba* was found to be unacceptable, the risk of fenbuconazole to aquatic vascular plants has not been determined at this time.

6.4.3.6 Summary of Risk to Aquatic Organisms

Several areas of concern have been identified for aquatic species following an assessment of the environmental safety associated with the use of fenbuconazole (Appendix IV, Table 6). Using the proposed pattern of 7 applications per year at a maximum rate of 0.105 kg a.i./ha, fenbuconazole poses a low acute risk to warmwater fish, freshwater algae and marine invertebrates. There is a low risk of effects in early-life stages of freshwater fish following exposure to fenbuconazole. Furthermore, the risk posed to freshwater benthic invertebrates (e.g., chironomids) based on exposure to fenbuconazole in water (i.e., pore water) or sediment has not been determined. Risks to benthic species may be present as a result of the partitioning of fenbuconazole to sediments. Although data were not submitted on the risk to marine benthic species, this risk may be expected to exceed that of the pelagic species of marine organism that was reviewed (mysid) because of the persistence of fenbuconazole in sediments. It should be noted, however, that exposure to marine organisms is expected to be limited in Canada as the areas in which stone fruits are grown are distant from marine waters. The potential risk to aquatic vascular plants has not been determined at this time. As for terrestrial organisms, the risks to aquatic organisms resulting from exposure to major transformation products of fenbuconazole are unknown.

6.5 Risk Mitigation

Environmental Concerns

Based on the data submitted and on the existing data requirements for Use-site Category 14 (Terrestrial Food Crops), several areas of concern were identified following an assessment of the environmental safety associated with the use of fenbuconazole. Application of fenbuconazole using the proposed pattern of 7 applications per year at a maximum rate of 0.105 kg a.i./ha will pose a potential risk to the following organisms:

Low Risk

- Upland game bird (Bobwhite quail)—Reproduction
- Wild mammals (rats)—Reproduction
- Bluegill sunfish—Acute
- Fathead minnow—Early-life stage
- Freshwater algae—Acute
- Marine invertebrates (Mysid)—It should be noted that, since the risk from exposure to fenbuconazole in marine sediment has not been assessed, the risk to

benthic species may exceed that for the pelagic species of marine invertebrate that was reviewed.

Moderate Risk

- Wild mammals (rats, mice)—Dietary

Unknown Risk

- Freshwater benthic invertebrates (chironomids)
- Aquatic vascular plants

Fenbuconazole is a persistent compound and limited environmental toxicity data have been reviewed. Very high amounts of carryover are expected. The PMRA recommends that this product not be applied in consecutive years to reduce the environmental loading of fenbuconazole. Toxicological concerns with the major transformation products are unknown.

Any further use expansion beyond stone fruit growing regions (e.g., Okanagan Valley, British Columbia, or the Niagara Region, Ontario) will require a re-evaluation of drinking water concentrations.

Buffer Zones

Based on the proposed application rates, buffer zones to protect sensitive terrestrial and aquatic habitats are not required.

Additional Required Label Statements

Under the ENVIRONMENTAL HAZARDS section, the statement "This product is toxic to fish." ("highly toxic" on the label for the technical grade active ingredient) on the labels for the technical active ingredient and end-use product must be replaced with the following:

> TOXIC to aquatic organisms.

On the label for the technical active ingredient, under the ENVIRONMENTAL HAZARDS section, delete the phrase "unless in accordance with the permitting authority"at the end of the second sentence so that the modified sentence reads as follows:

> Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters.

On the label for the technical grade active ingredient, under the ENVIRONMENTAL HAZARDS section, delete the following statement:

> Do not discharge effluent containing this product into sewer systems without previously notifying the sewage treatment plant authority.

Based on the persistence of fenbuconazole and high potential for carryover, which may detrimentally affect organisms, the following statement must be added to the ENVIRONMENTAL HAZARDS section of the label for the end-use product:

> Fenbuconazole is persistent and will carryover. It is recommended that any product containing fenbuconazole not be used in areas treated with this product during the previous season.

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended Use

Indar 75 WSP is proposed for application to stone fruit (USC 14) to control blossom blight and fruit brown rot of apricot, tart cherry and sweet cherry, nectarines, peaches and plums as well as leaf spot of tart cherry and sweet cherry, scab of peach and black knot of tart cherry and plum. The proposed use rate is 140 g product/500 L water/ha applied by ground (usually airblast) sprayer, with up to 2 sprays at early red bud through bloom stage, and a third coverspray pre-pick if needed. In addition it can be applied to fruit up to time of harvest but not postharvest, and may be applied to foliage after harvest for leaf spot only. Spray water volume varies considerably with size of trees and is calculated case-by-case to give optimum coverage while maintaining product rate per hectare.

Indar 75 WSP should be first applied prior to infection. It is proposed at spray intervals of 7 to 14 days depending on disease pressure, and can be applied up to day of harvest. The applicant has indicated that there can be up to eight spray dates per season but the typical number of applications is two per disease (see Table 7.1).

Table 7.1 Proposed Spray Schedule for Use of Indar on Stone Fruit in Canada

Crop/Disease	Bloom	Shuck	Cover I	Cover II	Cover III	Preharvest I	Preharvest II	Postharvest (leaves)	Typical no. of sprays
Apricot/nectarine/peach									
Blossom blight	X	X							1
Fruit brown rot						X	X		2
Cherries, sweet and tart									
Blossom blight	X	X							1
Fruit brown rot			X	X	X	X	X		2
Leaf spot			X	X	X			X	0
Cherries, tart									
Black knot		X	X	X	X				2
Peach									
Scab		X	X	X					0
Plums									
Fruit brown rot						X	X		2
Black knot	X	X	X	X	X				2

7.1.2 Mode of Action

Indar 75 WSP contains 75% fenbuconazole, a sterol inhibitor (Group 3) fungicide. Active ingredients in this group interfere with production of ergosterol for fungal membranes. Treated fungal spores will germinate but vegetative growth does not occur. Fenbuconazole is rapidly absorbed by green tissues and translocated acropetally.

7.1.3 Nature of Pest Problem

Blossom blight and fruit rot are a widespread and significant problem on stone fruit crops. In Canada, they are really two phases of a disease caused by the same or similar pathogens (*Monilinia* spp.), first causing infection of blossoms and twigs, and later decay of ripening fruit or harvested fruit, with up to 100% loss. Blossom blight symptoms are prevalent on peach, nectarine and apricot but less common on cherry or plum. Infected

plant parts, both on and off the tree, become a source of further inoculum that spreads during warm, wet weather. Fungicides are needed to reduce initial inoculum on blossoms, to protect fruit from later infection and to prevent rot in storage. The different crops each have their own critical period when coverage is most important, and only sweet cherries may require weekly sprays for the whole season. Fungicides are used primarily to control this disease, with additional sprays to control other diseases only if these are likely to be severe.

Black knot of sour cherry and plum is caused by *Dibotryon morbosum* and affects American, Japanese and European plum varieties as well as wild plums and cherries. Infection of shoots, twigs and branches occurs when spores are released in wet weather between early April and June. Lesions develop into cankers that may take two years to produce more spores. Cankers appear as black outgrowths resulting in progressive girdling of branches, death of parts of the tree and yield loss. Black knot is prevalent in Eastern Canada.

Leaf spot of cherry can cause defoliation before or after fruit, reduced flower and fruit production, and cause poor fruit quality. Subsequent yield losses may be 80–100%. Scab of peach causes superficial spots on the fruit, reducing marketability. These are less critical diseases in Canadian production than blossom blight, fruit brown rot or black knot.

7.1.4 Effectiveness Against Pest

Five reports of Canadian brown rot trials with Indar products (75 WSP or 240 g/L flowable) on peach, nectarine or sour cherry were provided. Blossom blight was not assessed directly but is reflected by the level of brown rot. In the untreated check, up to 17% of fruit on the tree showed symptoms, while after storage for 5–11 days 41–96% of fruit was affected. Indar provided 93–98% control of disease in stored fruit when applied alone (4–7 applications) and up to 83% when applied in a mixed program. Efficacy of Indar was consistently as good as or better than commercial standards including myclobutanil and is expected to have similar activity against brown rot on all stone fruits. These data support the application of Indar 75 WSP at a rate of 105 g a.i./ha to stone fruit beginning at early bloom in a program of 4 to 7 sprays, alone or alternated with other protectant fungicides.

One black knot trial on European plum and one on sour cherry were provided. In these trials, Indar was applied to inoculated trees at 100 or 135 g a.i./ha in May and June (4–5 sprays) before symptoms developed. The percentage of shoots infected with black knot was assessed the following spring. Indar provided 82–98% control, similar to Bravo and Captan, compared with 20–41% infected shoots in the untreated check.

Claims for cherry leaf spot and peach leaf scab were withdrawn by the applicant. As cherry leaf spot was the only disease requiring postharvest sprays to trees, there is no

need for this final (8th) application. The spray interval of up to 14 days is also not applicable. Claims of control of blossom blight, brown rot and black knot are accepted as proposed at 140 g a.i./ha.

In efficacy trials, initial sprays were described as percent bloom; however, more specific growth stages are used on the proposed label, consistent with the American label and presumably familiar to Canadian growers. There were insufficient comparative trials to determine a lowest effective rate; however, the proposed rate was shown to be effective for the 75 WSP formulation and is consistent with the rate used commercially in the United States.

From an efficacy standpoint, there is no restriction on the number of applications per season; however, Indar 75 WSP would typically be alternated with other products, resulting in a use pattern of up to four sprays per season, and would provide benefit whenever it is included in the spray program. Data were not submitted to confirm that a final spray on harvest day is necessary for control; therefore, a longer preharvest interval would also be acceptable.

7.2 Phytotoxicity to Target Plants (including different cultivars), or to Target Plant Products (OECD 7.4)

In field trials, slight phytotoxicity to peach blossoms was noted at one site where Indar 75 WSP plus surfactant were applied around a time of near-frost conditions in April. This did not affect fruit set or yield. The product has apparently been used in Europe and the United States without notable crop damage.

7.3 Observations on Undesirable or Unintended Side Effects (OECD 7.5)

Indar may be compatible with the biocontrol insects and arthropods used in orchards. It has been shown to have low toxicity to honeybees and was screened against five insect species (from Lepidoptera, Coleoptera and Homoptera) as well as the two-spotted spider mite (*Tetranychus urticae*) and green peach aphid (*Myzus persicae*) with no activity as a spray or soil application.

7.3.1 Impact on Succeeding Crops (OECD 7.5.1)

Not applicable to orchard use.

7.3.2 Impact on Adjacent Crops (OECD 7.5.2)

Indar was tested in orchards typically undersown with sod crops such as ryegrass, without any noted effect. Observations of other orchard crops which might be grown near stone fruits were not reported.

7.4 Economics

Approximately 5800 ha of stone fruits are grown in Ontario and British Columbia combined, which comprises 98% of the national crop (2001, Statistics Canada). Farm value in Ontario alone is $28 million, according to the applicant. Brown rot is the major disease affecting these crops and can cause up to 100% loss. This typically requires 5–10 fungicide applications per season for control, at an estimated cost of $40–$142 per hectare per spray, depending on the product used. For comparable cost, Indar 75 WSP will contribute to disease control and help maintain marketable quality and yields. Its value to the grower is in providing another effective disease control option.

7.5 Sustainability

7.5.1 Survey of Alternatives

The stone fruit diseases are currently managed by fungicides and sanitation. Some crops are less affected and certain varieties may have disease tolerance due to time of ripening or other physiological characteristics; however, resistant varieties are generally not available.

7.5.1.1 Non-chemical Control Practices

Both brown rot and black knot pathogens are capable of producing large numbers of spores and therefore removing as much infected material as possible is critical to managing disease. For example, any canker or infected shoot should be pruned out and general pruning should promote an open, ventilated canopy. Unharvested fruit should be removed from trees in autumn, when possible, thinning of fruit should be timed so that it decays quickly on the orchard floor, and cultivation under trees in spring may be used to disrupt fungal fruiting structures that develop. Culled fruit should not be piled in one area near to trees.

7.5.1.2 Chemical Control Practices

Registered products for these two diseases on stone fruit are as follows:

- captan;
- iprodione;
- chlorothalonil;
- sulphur;
- thiophanate-methyl;
- triforine,
- myclobutanil;
- propiconazole; and
- cyprodinil (see Table 7.5.1).

Application rates are in the range of 125–4500 g a.i. per application (18 kg for sulphur) and a program can include up to 10 sprays of different products per season. Individual products may have limitations with respect to effectiveness, crop safety or potential for resistance. The demethylation inhibitor products and iprodione are favoured for blossom blight control, whereas triforine and sulphur are rarely used.

Table 7.5.1 Alternative Disease Control Products

Active Ingredient	End-use Products Examples	Fungicide Activity Site	Application Rate (a.i./ha)		Comments
			Brown Rot	Black Knot	
Captan	Maestro, Captan	Multi-site	3–3.5 kg	3–3.5 kg	Poor rainfastness. Phytotoxic on certain sweet cherry and plum varieties.
Chlorothalonil	Bravo	Multi-site	2.5–4.5 kg	2.5–4.5 kg	Phytotoxic with oil.
Cyprodinil	Vanguard	Amino acids	280–560 g		Prone to resistance. Not for cherries.
Iprodione	Rovral	Cell division, DNA, RNA	750–875 g		Some postinfection activity. Resistance found in other regions.
Myclobutanil	Nova	Sterol demethylation	136 g		Also controls powdery mildew. Prone to resistance for other diseases. Not used for brown rot.
Propiconazole	Topas	Sterol demethylation	125 g		Some postinfection activity. Prone to resistance for other diseases.
Sulphur	Kumulus, MicroNiasul	Multi-site	18 kg		Harmful to some beneficial mites, can be phytotoxic, skin irritant.
Thiophanate-methyl	Senator, Easout	Tubulin formation	1.22 kg		Group is prone to resistance for brown rot.
Triforine	Funginex	Sterol demethylation	488 g		Prone to resistance for other diseases.

7.5.2 Compatibility with Current Management Practices Including IPM

Integrated pest management (IPM) practices are strongly recommended in Ontario and British Columbia. These include monitoring for inoculum of stone fruit diseases to determine the level of disease pressure. Although thresholds are not established for initial fungicide application, sampling of flowers, twigs and fruit for brown rot symptoms can provide feedback on effectiveness of spray programs and assist in decision-making regarding further applications during the season. Some products have postinfection activity and may prevent sporulation from recent infections, but it is best not to rely on this feature and to apply all products preventatively. Indar has been assessed in combination with captan and in sequence with other registered fungicides without apparent incompatibility, provided that the water-soluble pouches are dissolved in the spray mixture before other products are added as a tankmix.

Another aspect of IPM is to alternate use of fungicide chemical groups and reduce the number of sprays per season where possible. According to the applicant, Indar 75 WSP has a role in replacing one myclobutanil or triforine early spray and one captan or iprodione spray late in the season for brown rot control. By providing improved control, this may delay the need for frequent (3–7 day) applications of less effective protectants. As fenbuconazole is in the same chemical class as myclobutanil and propiconazole (sterol inhibitors), these three would not be used exclusively due to risk of promoting resistance, particularly for brown rot.

Indar has been shown to have low toxicity to honeybees, has no adverse effects on beneficial arthropods (*Aphidius rhoplosiphi, Typhlodromus pyri, Chrysoperla carnea and Poecilus cupreus*) and was screened against five insect species (from Lepidoptera, Coleoptera and Homoptera) as well as the two-spotted spider mite (*Tetranychus urticae*) and green peach aphid (*Myzus persicae*) with no activity as a spray or soil application. It may be compatible with the biocontrol insects and arthropods used in orchards. However, since it was not tested specifically against beneficial species, the impact of fenbuconazole on beneficial species in IPM programs cannot be determined at this time.

7.5.3 Contribution to Risk Reduction

Indar provides an alternative to current fungicide products, some of which may present greater hazards to human health and the environment.

7.5.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

The Fungicide Resistance Action Committee (FRAC) has not reported specific recommendations for stone fruit pathogens; however, general principles of resistance management should be included on the Indar 75 WSP label, as per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target*

Site/Mode of Action. Fenbuconazole is a Group 3 fungicide (demethylation inhibitors) and may be prone to resistance in pathogens that have been exposed to other fungicides in this group, such as myclobutanil and propiconazole. It is recommended that Indar 75 WSP be alternated with products from other fungicide groups, such as captan, iprodione and cyprodinil, rather than with other Group 3 products.

The following statements are required on the Indar 75 WSP label:

"

GROUP	3	FUNGICIDE

For resistance management, please note that Indar 75 WSP contains a Group 3 fungicide. Any fungal population may contain individuals naturally resistant to Indar 75 WSP and other Group 3 fungicides. A gradual or total loss of pest control may occur over time if these fungicides are used repeatedly in the same orchards. Other resistance mechanisms that are not linked to site of action but are specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed."

To delay fungicide resistance:

"Where possible, rotate the use of Indar 75 WSP or other Group 3 fungicides with different groups that control the same pathogens.

Avoid application of consecutive sprays of Indar 75 WSP or other fungicides in the same group in a season.

Fungicide use should be based on an IPM program that includes scouting, historical information related to pesticide use and cover crop, and that considers cultural, biological as well as other chemical control practices.

Monitor treated fungal populations for resistance development.

If disease continues to progress after treatment with this product, do not increase the use rate. Discontinue use of this product and switch to another fungicide with a different site of action, if available.

Contact your local extension specialist or certified crop advisors for any additional pesticide resistance management or IPM recommendations for specific crops and pathogens.

For further information and to report suspected resistance, contact Dow AgroSciences Canada Inc. at 1 800 667-3852."

7.6 Conclusions

Indar 75 WSP is effective for control of blossom blight and fruit brown rot on apricot, peach, nectarine, plum and cherry and for control of black knot on plum and cherry. Indar 75 WSP may be applied at a rate of 140 g per hectare from early red bud stage up to day of harvest. The maximum number of applications is seven per season; however, for resistance management, Indar 75 WSP should be alternated with products from different fungicide activity groups. For comparable cost, Indar 75 WSP will contribute to disease control and help maintain marketable quality and yields. Its value to the grower is in providing another effective disease control option.

7.6.1 Summary

Table 7.6.1 Summary of Label Proposals and Recommendations

Proposed		Recommendation (based on value assessment)
Crops/Diseases	Crop Group 12 stone fruits: apricot, sweet cherry, tart cherry, nectarine, peach, chickasaw plum, damson plum, Japanese plum and fresh prune—fruit brown rot and blossom blight.	As proposed
	Tart cherry, Japanese plum, chickasaw plum, damson plum, and fresh prune—black knot.	As proposed
Rate	140 g/ha (1 pouch per 0.4 hectares) in 500 L of water or sufficient water to ensure thorough coverage.	As proposed
Application Method	Add a wetting agent or non-polymer spray adjuvant. Ground application only.	As proposed Add contraindication for aerial
Timing of Applications	Blossom blight—begin at early red bud stage before infection occurs. Fruit Brown Rot—begin applications 3 weeks before harvest using a 7–10 day spray interval. Black knot—begin at petal fall (cherry) or white popcorn stage (plum). Apply every 7 to 10 days. Under high disease pressure or favourable weather conditions, use shortest spray interval.	As proposed

Proposed		Recommendation (based on value assessment)
Conditions	Do not use more than 8 applications per season. May be applied up to day of harvest.	Do not use more than 7 applications per season (or as per residue data). Preharvest interval of 1 day also acceptable

8.0 Toxic Substances Management Policy Considerations

During the review of **Indar 75WSP**, the PMRA has taken into account the federal Toxic Substances Management Policy[1] and has followed its Regulatory Directive DIR99-03[2]. It has been determined that this product does not meet TSMP Track 1 criteria because of the following:

- **Fenbuconazole** is not bioaccumulative. Studies have shown that the bioconcentration factor (BCF) is 330, which is below the TSMP Track 1 cut-off criterion of BCF ≥5000. Furthermore, the *n*-octanol–water partition coefficient (log K_{ow}) is 3.22 ± 0.08, which is below the TSMP Track 1 cut-off criterion of ≥5.0.

- **Fenbuconazole** (technical grade) does not contain any impurity known to be a toxic microcontaminant as identified in Part 2.13.4 of Regulatory Directive DIR98-04, *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*, or any of the TSMP Track 1 substances listed in Appendix II of Regulatory Directive DIR99-03. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

The end-use product is not known to contain any USEPA inert List 1 or 2 formulants or any known TSMP Track 1 substances.

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1 The federal Toxic Substances Management Policy is available through Environment Canada's website at www.ec.gc.ca/toxics.

2 Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, is available through the Pest Management Information Service. Phone: 1 800 267-6315 within Canada or (613) 736-3799 outside Canada (long distance charges apply); Fax: (613) 736-3798; E-mail: pmra_infoserv@hc-sc.gc.ca; or through our website at www.pmra-arla.gc.ca

9.0 Regulatory Decision

The PMRA has carried out an assessment of available information in accordance with the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value of the active ingredient fenbuconazole and the end-use product Indar 75 WSP Fungicide. The Agency has concluded that the use of the active ingredient fenbuconazole and the end-use product Indar 75 WSP Fungicide in accordance with the label has merit and value consistent with the Pest Control Products Regulations and does not entail an unacceptable risk of harm. Based on the considerations outlined above, therefore, the use of the active ingredient fenbuconazole and the end-use product Indar 75 WSP Fungicide, for the control of the control of blossom blight, fruit brown rot and black knot on stone fruit group (apricot, sweet cherry, tart cherry, nectarine, peach, plum, chickasaw plum, damson plum, Japanese plum and fresh prune), is proposed for full registration, pursuant to the Pest Control Products Regulations.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

List of Abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ALAT	alanine aminotransferase
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
BCF	bioconcentration factor
bw	body weight
BWI	body weight per individual
CAS	Chemical Abstracts Service
d	day(s)
DACO	Data Code
DFR	dislodgeable foliar residue
DI	daily intake
DNA	deoxyribonucleic acid
DRA	dietary risk assessment
DT_{50}	decline time 50%
dw	dry weight
EC_{50}	effect concentration 50%
EEC	expected environmental concentration
EXAMS	Exposure Analysis Modelling System
F_1	1st generation offspring
FC	food consumption
FRAC	Fungicide Resistance Action Committee
g	gram
GAP	good agricultural practices
GC	gas chromatography
GSD	geometric standard deviation
ILV	independent laboratory validation
IPM	integrated pest management
IUPAC	International Union of Pure and Applied Chemistry
K_d	adsorption quotient
K_{oc}	adsorption quotient normalized to organic carbon
K_{ow}	*n*-octanol–water partition coefficient
L	litre
LADD	lifetime average daily dose
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LEACHM	Leaching Estimation and Chemistry Model
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEC	lowest observed effect concentration
LOQ	limit of quantification

LR	lethal rate
MAS	maximum average score
mg	milligram
mL	millilitre
MMAD	mass median aerodynamic diameter
MOE	margin of exposure
MOS	margin of safety
MRL	maximum residue limit
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
OECD	Organisation for Economic Cooperation and Development
PDI	potential daily intake
pH	$\log_{10}$ hydrogen ion concentration
PHED	Pesticide Handlers' Exposure Database
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
ppm	parts per million
PRZM	Pesticide Root Zone Model
Q_1*	human risk
RAC	raw agricultural commodity
RNA	ribonucleic acid
ROC	residue of concern
RSD	relative standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamate pyruvate transaminase
SPE	solid phase extraction
SPSF	Statement of Product Specification Form
STMR	Supervised Trial Median Residue
T3	tri-iodothyronine
T4	thyroxine
TOC	total organic carbon
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
UF	uncertainty factor
µg	microgram
µL	microlitre
U.S.	United States
USC	Use Site Category
USEPA	United States Environmental Protection Agency
UV	ultraviolet

Appendix I Summary Table of Toxicology Studies for Fenbuconazole

METABOLISM—TECHNICAL

In a series of rat metabolism studies, ^{14}C-RH-7592 (≥98% radiochemical purity) uniformly labelled in the unsubstituted phenyl ring, was administered to Sprague Dawley rats (3–5/sex/dose) as a single gavage dose at 1 or 100 mg/kg bw or as a repeated gavage dose of 14 daily doses (10 ppm in the diet) of unlabelled RH-7592 (purity 96.4%) followed by a single oral dose of 1 mg/kg bw of ^{14}C-RH-7592 on day 15. In addition, another group of bile duct-cannulated rats (5 rats/sex) received a single gavage dose of ^{14}C-RH-7592 at 1 mg/kg bw.

Following oral dosing, ^{14}C-RH-7592 was rapidly absorbed, distributed and excreted. The feces was the major route of excretion, accounting for ~76% to 94% of the administered dose. Recovery from urine ranged from ~5% to 14%. The majority of the radioactivity was excreted within 24 to 48 hours postdosing. Biliary excretion data indicated that systemic absorption of RH-7592 was high for all dosing groups. Tissue distribution and bioaccumulation were minimal, with <1% of the administered dose recovered in tissues at 96 hours. Radioactivity in the blood peaked at 3 to 6 hours. Elimination was biphasic with an initial rapid phase (24–48 hours postdosing) followed by a slower decline (48–96 hours postdosing). There was no sex- or dose-related difference in absorption, distribution or elimination.

There were many metabolites in excreta, indicating extensive metabolic breakdown. All major metabolites were derived from enzymatic oxidations on either the benzylic carbon alpha to the chlorophenyl ring or the 3- or 4-position of the phenyl ring. Subsequent non-enzymatic cyclization of the newly formed benzylic alcohol with the adjacent nitrile group, followed by hydrolysis led to the iminolactone/lactone family of metabolites. Conjugation of the OH groups of the alcohol and phenols led to more metabolites, as did combinations of the above-mentioned reactions. A minor metabolic pathway was the cleavage of RH-7592 to give triazole and RS-5922. There was no significant difference in the total metabolite profile for male and female rats, although some metabolites were present in greater quantities in males, and vice versa. There was a dose-related difference in metabolism, with a higher amount of unmetabolized parent compound in the feces of the high-dose group, compared to the low-dose and repeated-dose groups, indicating that saturation of the metabolic pathway may be occurring at the high dose.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/COMMENTS
ACUTE STUDIES—TECHNICAL			
Oral	Mouse—CD-1, 5/sex/group; 0 and 5000 mg/kg bw	LD_{50}>5000 mg/kg bw	No treatment-related finding **LOW TOXICITY**
Oral	Rat—Crl:CD BR, 5/sex/group; 1, 2, 3, 4, and 5 g/kg bw	LD_{50}>5 g/kg bw	**≥1 g/kg bw:** Lower body-weight gain, both sexes, week 1 only **≥2 g/kg bw:** Ataxia, lacrimation, salivation, passiveness and arched back. Recovery was complete by day 8. **5 g/kg bw:** One male and 2 females died; reddened glandular stomach and enlarged adrenal glands at necropsy. **LOW TOXICITY**
Dermal	Rat—Crl:CD BR, 5/sex/group; 0 and 5000 mg/kg bw	LD_{50}>5000 mg/kg bw	No treatment-related finding No skin irritation **LOW TOXICITY**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/COMMENTS
Inhalation	Rat—Sprague-Dawley, 5/sex; 2.1 mg/L	LC_{50} >2.1 mg/L	MMAD = 9.8 µm, GSD not calculated; however, 18.6% of particles < 3 µm. Clinical observations observed were apathy, hunched posture, laboured respiration, piloerection, and chromodacryorrhea. Complete recovery by study day 3. **LOW TOXICITY**
Skin irritation	Rabbit—NZW, 3/sex; 0.5 g dose	MAS = 0.00/8.0	**NON-IRRITATING**
Eye irritation	Rabbit—NZW, 9 males; 0.1 g dose	MAS = 0.00/110	**MINIMALLY IRRITATING**
Skin sensitization (Buehler closed patch method)	Guinea pig—Hartley; 10/sex in test group, 5/sex in positive and negative control groups. Test material administered 25% for induction and 20% for challenge. Positive control DNCB	Test material did not elicit any dermal reaction. No evidence of sensitization Positive control was sensitizing, demonstrating responsiveness of assay.	**NOT A SENSITIZER**
ACUTE STUDIES—FORMULATION (INDAR 75WP)			
Oral	Rat—Crl: CD BR, 5/sex/group; 1, 2, 3, 4, and 5 g/kg bw	Combined LD_{50}>4 g/kg bw (confidence limits of 3.6 and 4.5 g/kg bw).	**1 g/kg bw:** Lower body-weight gain, study week 1, males only **≥ 2 g/kg bw:** Treatment-related mortality; lower body-weight gain, both sexes, week 1 only. Ataxia, lacrimation, passiveness, yellow/brown-stained ano-genital area, unthrifty appearance, reddened extremities and arched back; recovery was complete by day 7. Necropsy findings (decadents only): reddened intestines and stomach, black/red areas attached to the mucosal surface of the stomach. **LOW TOXICITY**
Dermal	Rat—Crl: CD BR, 6/sex; 2 g/kg bw	LD_{50}> 2 g/kg bw	Reddened skin, tan stained skin, dessication and pinpoint scabs first observed on study day 1 with complete recovery by day 11. **LOW TOXICITY**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/COMMENTS
Inhalation	Rat—Sprague-Dawley, 5/sex; 4.4 mg/L	LC_{50} > 4.4 mg/L	MMAD = 2.62 µm, GSD = 1.76 µm. Ruffled fur, both sexes; red serous secretion from the nose and laboured breathing, females only. Complete recovery by day 3. White gray/black brown/dark red foci on the lungs (all males, 1 female). **LOW TOXICITY**
Skin irritation	Rabbit—NZW, 6 males; 0.5 g dose	MAS = 0.17/8.0	Very slight erythema that cleared by 24 hours. Treatment did not result in edema. **MINIMALLY IRRITATING**
Eye Irritation	Rabbit—NZW, 6 males; 0.1g dose	MAS = 3.3/110	Slight conjunctival irritation, cleared by 48 hours. Treatment did not affect the cornea or iris. **MINIMALLY IRRITATING**
Skin sensitization (Buehler closed patch procedure)	Guinea pig—Hartley; 10/sex in test group, 5/sex in positive and negative control groups. Test material administered 20% for induction and for challenge. Positive control DNCB	Test material did not elicit any evidence of sensitization. Positive control was sensitizing, demonstrating responsiveness of assay.	**NOT A SENSITIZER**
SHORT TERM—TECHNICAL			
28-day dermal	Rats—Crl: CD BR 6/sex/group; No treatment (sham control), RH-57592 formulation blank, RH-57592 technical at 1.0 g a.i./kg bw/day, RH-57592 2F at 0.0625 g a.i./kg bw/day, RH-57592 2F at 0.25 g a.i./kg bw/day or RH-57592 2F at 1.0 g a.i./kg bw/day	**Systemic toxicity:** LOAEL could not be determined since there were no treatment-related systemic effects. NOAEL = 1.0 g a.i./kg bw/day. **Dermal toxicity:** LOAEL could not be determined since there were no treatment-related systemic effects. NOAEL = 1.0 g a.i./kg bw/day.	No systemic treatment-related effects at any dose level tested. **Dermal findings**: Acanthosis, parakeratosis, eschar or superficial exudate, and necrosis of the epidermis. These findings were attributed to the non-active ingredients of the 2F formulation and not to the active ingredient itself.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/COMMENTS
3-month dietary	Mouse—CD-1; 10/sex/group; 0, 540, 1000, 3000 and 10 000 ppm (equal to 0, 85.59, 158.40, 465.37 and 964.01 mg/kg bw/day for males, and 0, 113.46, 201.93, 595.30 and 2014.99 mg/kg bw/day for females) Compound consumption in the 10 000 ppm group is based on data from the first 2 weeks of the study only because of treatment-related mortality.	LOAEL = 85.59/113.46 mg/kg bw/day NOAEL could not be determined since there were treatment-related effects observed at all dose levels tested.	**85.59/113.46, 158.40/201.93 and 465.37/595.30 mg/kg bw/day:** Decreased body-weight gain (465.37 only; males); increased liver weights; hepatocyte hypertrophy, hepatocyte vacuolation and hepatocyte necrosis; decreased triglycerides; decreased cholesterol; increased ALAT (465.37 only; males) **964.01/2014.99 mg/kg bw/day:** Not tolerated. Resulted in 80% and 100% mortality for males and females, respectively, by study week 3.
3-month dietary	Mouse—CD-1; 10/sex/group; 0, 20, 60, 180, and 540 ppm (equal to 0, 3.8, 11.1, 28.6, and 99.1 mg/kg bw/day for males, and 0, 5.7, 17.6, 50.4, and 139.2 mg/kg bw/day for females).	**Males:** LOAEL = 28.6 mg/kg bw/day NOAEL = 11.1 mg/kg bw/day Females: LOAEL = 139.2 mg/kg bw/day NOAEL = 50.4 mg/kg bw/day	**3.8/5.7 and 11.1/17.6 mg/kg bw/day:** No treatment-related finding **28.6 mg/kg bw/day:** Males only affected—increased liver weight, hepatocyte hypertrophy and single cell necrosis; increased SGPT **99.1/139.2 mg/kg bw/day:** Increased liver weight, hepatocyte hypertrophy and vacuolation; focal/single cell necrosis; increased SGPT and SGOT
3-month dietary	Rat—Crl:CD BR;10/sex/group; 0, 20, 80, 400, and 1600 ppm (equal to 0, 1.3, 5.1, 25.3, and 103.0 mg/kg bw/day for males, and 0, 1.5, 6.3, 31.5, and 123.9 mg/kg bw/day for females)	**Males**: LOAEL = 5.1 mg/kg bw/day NOAEL = 1.3 mg/kg bw/day **Females:** LOAEL = 31.5 mg/kg bw/day NOAEL = 6.3 mg/kg bw/day	**1.3/1.5 mg/kg bw/day:** No treatment-related findings **5.1 mg/kg bw/day:** Males only affected—hepatocyte vacuolation **25.3/31.5 mg/kg bw/day:** Increased liver weight; hepatocyte hypertrophy and vacuolation **103.0/123.9 mg/kg bw/day:** Decreased body-weight gain (females only); increased liver weight; hepatocyte hypertrophy and vacuolation; decreased triglycerides; increased cholesterol and GGT (females only); follicular cell hypertrophy in the thyroid

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/COMMENTS
3-month dietary	Dog—Beagle; 4/sex/group; 0, 30, 100, 400, and 1600 ppm (equal to 0, 0.97, 3.30, 13.27, and 50.40 mg/kg bw/day for males, and 0, 1.05, 3.48, 13.98, and 53.27 mg/kg bw/day for females)	LOAEL = 13.27/13.98 mg/kg bw/day NOAEL = 3.30/3.48 mg/kg bw/day	**0.97/1.05 and 3.30/3.48 mg/kg bw/day:** No treatment-related findings **13.27/13.98 mg/kg bw/day:** Increased liver weight; hepatocyte vacuolation (males only); hepatocyte hypertrophy **50.40/53.27 mg/kg bw/day:** Decreased body-weight gain, food intake and food efficiency; increased liver weight; hepatocyte hypertrophy; increased alkaline phosphatase; increased SGPT and GGT (females only); decreased total protein, albumin and globulin (females only); increased triglycerides (males only); marginally decreased RBC count, Hgb and HCT (females only)
1-year dietary	Dog—Beagle; 4/sex/group; 0, 15, 150, and 1200 ppm (equal to 0, 0.54, 5.2, and 47.8 mg/kg bw/day for males, and 0, 0.62, 5.2, and 46.4 mg/kg bw/day for females).	LOAEL = 47.8/46.4 mg/kg bw/day NOAEL = 5.2 mg/kg bw/day	**0.54/0.62 and 5.2 mg/kg bw/day:** No adverse treatment-related effects **47.8/46.4 mg/kg bw/day:** Decreased body-weight gain; increased liver, thyroid and adrenal weights; hepatocyte hypertrophy; hepatocyte pigment; increased alkaline phosphatase; decreased total protein and albumin

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/COMMENTS
CHRONIC TOXICITY/ONCOGENICITY—TECHNICAL			
78-week dietary	Mouse—CD-1 mice, 60/sex/group; 0, 10, 200 and 650 ppm for males (equal to 0, 1.28, 26.28 and 85.26 mg/kg bw/day) and 0, 10, 650 and 1300 ppm for females (equal to 0, 1.59, 104.64 and 208.84 mg/kg bw/day)	**Chronic effects** Males: LOAEL = 26.28 mg/kg bw/day NOAEL = 1.28 mg/kg bw/day Females: LOAEL = 104.64 mg/kg bw/day NOAEL = 1.59 mg/kg bw/day **Oncogenicity** Males: An increased incidence of hepatocellular carcinomas was noted at 85.26 mg/kg bw/day. Females: An increased incidence of hepatocellular adenomas and combined adenomas and carcinomas was noted at 208.84 mg/kg bw/day	**1.28/1.59 mg/kg bw/day:** No adverse treatment-related effects **26.28 mg/kg bw/day (males):** Increased liver weight; hepatocyte enlargement and vacuolization **85.26/104.64 mg/kg bw/day:** Increased liver weight; enlarged livers (males only); hepatocyte enlargement and vacuolization **208.84 mg/kg bw/day (females):** Increased liver weight; enlarged livers; hepatocyte enlargement and vacuolization
2-year dietary	Rat—Sprague-Dawley, 70/sex/group; 0, 8, 80 and 800 ppm (equal to 0, 0.30, 2.91 and 29.46 mg/kg bw/day for males and 0, 0.38, 3.89 and 42.29 mg/kg bw/day for females)	**Chronic effects** LOAEL = 29.46/42.29 mg/kg bw/day NOAEL = 2.91/3.89 mg/kg bw/day **Oncogenicity** **Males:** An increased incidence of thyroid follicular cell adenomas and combined thyroid follicular cell adenomas and carcinomas was noted at 29.46 mg/kg bw/day. **Females:** No evidence of treatment-related oncogenicity	**0.30/0.38 mg/kg bw/day and 2.91/3.89 mg/kg bw/day:** No adverse treatment-related effects **29.46/42.29 mg/kg bw/day:** Decreased body-weight gain (males only); increased liver and thyroid weights; increased cholesterol (females); enlarged thyroid (males); hepatocyte enlargement and vacuolization; thyroid focal cystic hyperplasia (males)

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/COMMENTS
2-year dietary; supplementary study	Male rats—Sprague-Dawley, 60/sex/group; 0, 800 and 1600 ppm (equal to 0, 28.87 and 62.07 mg/kg bw/day)	**Chronic effects** LOAEL = 28.87 mg/kg bw/day NOAEL could not be determined since there were treatment-related findings at both dose levels tested **Oncogenicity** An increased incidence of thyroid follicular cell adenomas and combined thyroid follicular cell adenomas and carcinomas was noted at 62.07 mg/kg bw/day	**28.87 mg/kg bw/day:** Decreased food efficiency; increased liver weight; hepatocyte enlargement and vacuolization; increased cholesterol **62.07 mg/kg bw/day:** Decreased body-weight gain; decreased food efficiency; increased liver weight; hepatocyte enlargement and vacuolization; thyroid follicular cell hypertrophy; increased cholesterol. (Decreased plasma thyroxine, week 103; increased TSH, weeks 85 and 103)

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/COMMENTS
REPRODUCTION/DEVELOPMENTAL TOXICITY—TECHNICAL			
Two-generation dietary, one litter per generation	Rat—Crl:CD BR, 25/sex/group; 0, 8, 80 and 800 ppm (equal to 0, 0.6, 5.8 and 61.3 mg/kg bw/day for males, and 0, 0.6, 6.4 and 66.4 mg/kg bw/day for females)	**Systemic Toxicity** LOAEL= 61.3/66.4 mg/kg bw/day NOAEL=5.8/6.4 mg/kg bw/day **Reproductive toxicity** **Males:** LOAEL could not be determined since there were no treatment-related effects at any dose level tested NOAEL = 61.3 mg/kg bw/day **Females:** LOAEL = 66.4 mg/kg bw/day NOAEL = 6.4 mg/kg bw/day **Offspring toxicity** LOAEL = 61.3/66.4 mg/kg bw/day NOAEL = 5.8/6.4 mg/kg bw/day	**0.6 mg/kg bw/day:** No treatment-related effects **6.4 mg/kg bw/day (females):** Slightly increased liver weight (P_2 females only; non-adverse) **61.3/66.4 mg/kg bw/day:** Mortality (females only); decreased body-weight gain and food intake; increased liver weight; increased thyroid weight (males); increased adrenal weight (females); hepatocyte hypertrophy and vacuolation; thyroid follicular cell hypertrophy; hypertrophy of zona glomerulosa of the adrenal (P_1 females; P_2 males and females) **Males:** No treatment-related reproductive effect at any dose level tested **Females:** **66.4 mg/kg bw/day:** Decreased number delivering; decreased litter size; decrease in the number and percentage of dams with liveborn pups; decreased gestation index; increase in the number and percentage of dams with stillborn pups; increase in number of litters with no viable offspring (P_1 only) **61.3/66.4 mg/kg bw/day:** Lower pup viability; lower pup body weight

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/COMMENTS
Teratogenicity oral gavage	Female rats—Crl: CD BR, 25/group; 0, 30, 75 or 150 mg/kg bw/day.	**Maternal toxicity** LOAEL = 75 mg/kg bw/day NOAEL = 30 mg/kg bw/day	**30 mg/kg bw/day:** No treatment-related effects **75 mg/kg bw/day:** Alopecia; scant feces; lower body weight and body-weight gain; lower corrected body weight and body-weight gain; lower gravid uterus weight **150 mg/kg bw/day:** Alopecia; scant feces; thin appearance; red vaginal discharge; lower body weight and body-weight gain; lower corrected body weight and body-weight gain; lower gravid uterus weight
		Developmental toxicity LOAEL = 75 mg/kg bw/day NOAEL = 30 mg/kg bw/day	**30 mg/kg bw/day:** No treatment-related effect **75 mg/kg bw/day:** Decreased number of live fetuses; increased postimplantation loss; increase in partially or unossified sternebrae **150 mg/kg bw/day:** Decreased number of live fetuses; increased postimplantation loss; increase in resorptions; lower fetal body weight; increase in rudimentary 14th ribs; increase in partially or unossified sternebrae; increase in partially or unossified pubes
		Teratogenicity LOAEL could not be determined since there were no treatment-related findings NOAEL = 150 mg/kg bw/day	No treatment-related teratogenic effects were noted at any dose level tested

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/COMMENTS
Teratogenicity oral gavage	Female rabbits—NZW, 20/group; 0, 10, 30 and 60 mg/kg bw/day.	**Maternal toxicity** LOAEL = 30 mg/kg bw/day NOAEL = 10 mg/kg bw/day **Developmental toxicity** LOAEL = 60 mg/kg bw/day NOAEL = 30 mg/kg bw/day **Teratogenicity** LOAEL could not be determined since there were no treatment-related findings NOAEL = 30 mg/kg bw/day	**10 mg/kg bw/day:** No treatment-related effects **30 mg/kg bw/day:** Decreased food intake; anorexia; soft or scant feces **60 mg/kg bw/day:** Mortality; loss in body weight; decreased food intake; abortions; anorexia and soft or scant to no feces; red discharge **10 and 30 mg/kg bw/day:** No treatment-related effects **60 mg/kg bw/day:** Abortions and total resorption of litters (increased postimplantation loss) No treatment-related teratogenic effects were noted at any dose level tested. **NOTE:** A meaningful evaluation of soft tissue, visceral, or skeletal effects could not be conducted in the 60 mg/kg bw/day group (maternally toxic dose level) since only one litter was produced.
MUTAGENICITY—TECHNICAL			
STUDY	**SPECIES/STRAIN or CELL TYPE**	**DOSES EMPLOYED**	**SIGNIFICANT EFFECTS/COMMENTS**
Bacillus subtilis, mammalian activation recombination repair assay	*B. subtilis*, strains H17 (rec+) and M45 (rec-)	625, 1250, 2500, 5 000, 10 000, and 50 000 µg/40 µL/plate, ± S9	Negative
S. typhimurium, mammalian activation gene mutation assay	*S. typhimurium*— TA 98, TA 100, TA 1535 and TA 1537	**Assay 1:** 50, 200, 500, 2000, and 5000 µg/plate, ± S9 **Assay 2:** 30, 50, 90, 160, and 300 µg/plate for strains TA100, TA1535, and TA1537, ± S9	Negative
S. typhimurium, mammalian activation gene mutation assay	*S. typhimurium*— TA 98, TA 100, TA 1535 and TA 1537	**Assay 1:** 20, 50, 200, 500, and 2000 µg/plate, ± S9 **Assay 2:** 160, 300, 500, 900, and 1600 µg/plate, + S9; 30, 50, 90, 160, and 300 µg/plate, -S9	Negative

STUDY	SPECIES/STRAIN or CELL TYPE	DOSES EMPLOYED	SIGNIFICANT EFFECTS/COMMENTS
S. typhimurium, mammalian activation gene mutation assay	*S. typhimurium*— TA 98, TA 100, TA 1535 and TA 1537	**Assay 1:** 50, 200, 500, 2000 and 5000 µg/plate, ± S9 **Assay 2:** 30, 50, 90, 160 and 300 µg/plate for strains TA1535 and TA1537, ± S9. 0.2, 0.5, 2, 5 and 20 µg/plate for strain TA98, ± S9 160, 300, 500, 900 and 1600 µg/plate for strain TA100, ± S9	Negative.
E. coli, mammalian activation gene mutation assay	*Escherichia coli*, strain WP2uvrA	156.25, 312.5, 625, 1250, 2500 and 5000 µg/plate, ± S9	Negative
Gene mutation assay	Chinese Hamster Ovary (CHO) cells	**Assay 1:** 10, 20, 30, 40 and 50 µg/mL, -S9 10, 35, 45 and 60 µg/mL, + S9 **Assay 2:** 15, 20, 25, 30, 35 and 40 µg/mL, -S9 30, 40, 45, 50, 55 and 60 µg/mL, +S9	Negative
Gene mutation assay	CHO cells	0, 3, 5, 10, 20 and 30 µg/mL, ± S9	Negative
Micronucleus assay, in vivo	Rat bone marrow cells	0 (vehicle control), 0.25, 1.25 and 2.5 g/kg bw, 15 rats/sex/group	Negative
Unscheduled DNA Synthesis	Rat Primary Hepatocytes	2.5, 5.0, 7.5, 10.0, 12.5 and 15.0 µg/mL	Negative
MUTAGENICITY—RH-11929			
S. typhimurium, mammalian activation gene mutation assay	*S. typhimurium*— TA 98, TA 100, TA 1535, and TA 1537	0, 156.25, 312.5, 625, 1250, 2500 and 5000 µg/plate, ± S9	Negative
MUTAGENICITY—RH-11930			
S. typhimurium, mammalian activation gene mutation assay	*S. typhimurium*— TA 98, TA 100, TA 1535 and TA 1537	0, 31.25, 62.5, 125, 250, 500 and 1000 µg/plate for strains TA100, TA1535, and TA 1537, ± S9 0, 156.25, 312.5, 625, 1250, 2500 and 5000 µg/plate for strain TA98, ± S9	Negative

STUDY	SPECIES/STRAIN or CELL TYPE	DOSES EMPLOYED	SIGNIFICANT EFFECTS/COMMENTS
SPECIAL STUDIES—TECHNICAL			
Hepatic effects, 4-week feeding study	Female mice—CD-1, 10/sex/group; 0, 20, 60, 180, and 1300 ppm (equal to 0, 5.2, 13.6, 47.4 and 323.6 mg/kg bw/day) Positive control phenobarbital, 230.0 mg/kg bw/day Male rats—Crl:CD BR, 10/sex/group, 0 or 1600 ppm (equal to 0 and 130.0 mg/kg bw/day) Positive control phenobarbital, 86.9 mg/kg bw/day	**Liver effects:** LOAEL = 180 ppm (equal to 47.4 mg/kg bw/day) NOAEL = 60 ppm (equal to 13.6 mg/kg bw/day)	**Mice:** **5.2 and 13.6 mg/kg bw/day:** No treatment-related effects **47.4 mg/kg bw/day:** ↑ cytochrome P_{450} (CYP2B); ↑ PROD activity. **323.6 mg/kg bw/day and phenobarbital:** Increased liver weight; liver histopathology; hepatocyte proliferation (week 1 only); ↑ cytochrome P_{450} (CYP2B); ↑ cytochrome b_5; ↑ PROD activity **Rats:** **130.0 mg/kg bw/day and phenobarbital:** Increased liver weight; liver histopathology; ↑ cytochrome P_{450} (CYP2B); ↑ cytochrome b_5; ↑ PROD activity. **After a 6-week recovery period:** Complete reversibility for all noted effects in mice and rats related to treatment with RH-7592 and phenobarbital
Thyroid function and hepatic clearance of thyroxine, 13-week feeding study	Male rats—Crl: CD BR, 10–20/group; 0, 8, 800, 1600 and 3200 ppm (approximately* equal to 0, 0.6, 57.9, 115.9 and 231.2 mg/kg bw/day). (*mg/kg bw/day determinations are approximate since values were calculated from data obtained from study weeks 1, 2, 3, 4, 5, 8 and 13 only.)	**Thyroid function:** LOAEL = 57.9 mg/kg bw/day NOAEL = 0.6 mg/kg bw/day	**0.6 mg/kg bw/day:** No treatment-related effects **57.9 mg/kg bw/day:** Increased liver and thyroid weights; hyperplasia/hypertrophy of thyroid follicular cells; ↑TSH (week 4) **115.9 mg/kg bw/day:** Decreased body-weight gain; increased liver and thyroid weights; hyperplasia/hypertrophy of thyroid follicular cells; ↑TSH (week 4); ↓T_4 (week 13) **231.2 mg/kg bw/day:** Decreased body-weight gain; increased liver and thyroid weights; hyperplasia/hypertrophy of thyroid follicular cells; ↑TSH (weeks 4 and 13); ↓T_4 (weeks 4 and 13); ↓rT_3 (week 4); ↑ biliary excretion of T_4 **After a 9-week recovery period:** Complete reversibility for all noted effects in rats related to treatment with RH-7592

STUDY	SPECIES/STRAIN or CELL TYPE	DOSES EMPLOYED	SIGNIFICANT EFFECTS/COMMENTS

Recommendation for ADI: 0.0128 mg/kg bw/day, based on the lowest NOAEL of 1.28 mg/kg bw/day in the mouse oncogenicity study, and using a 100-fold safety factor. This provides MOS of 500× for reproductive toxicity.

Recommendation for ARfD: For females 13+ years: 0.10 mg/kg bw/day, based on the lowest NOAEL of 30 mg/kg bw/day in the rat and rabbit teratology studies, and using a 300-fold uncertainty factor. This is based on the standard uncertainty factor of 100 with an additional 3-fold uncertainty factor due to the severity of the toxicological endpoint, i.e., increased postimplantation loss and a decrease in the number of live fetuses/litter.

There is no indication of increased susceptibility of rat or rabbit fetuses to in utero and/or postnatal exposure in the developmental and reproductive toxicity studies.

Carcinogenicity: There was evidence of oncogenic/carcinogenic potential of fenbuconazole in rodents. For rats, there was an increased occurrence of thyroid follicular cell benign tumours and combined thyroid follicular cell benign and/or malignant tumours in males (28.87 mg/kg bw/day). For mice, this was based on the occurrence of an increased trend for malignant liver tumours in males (85.26 mg/kg bw/day) and an increase in benign liver tumours and combined benign and/or malignant liver tumours in females (208.84 mg/kg bw/day). The proposed mechanistic pathway for the thyroid tumours in rats was scientifically supported by sound mechanistic data, i.e., prolonged stimulation of the thyroid by TSH leads to chronic follicular hypertrophy/hyperplasia, progressing to follicular neoplasia of the thyroid. However, the proposed mechanistic pathway for the liver tumours in mice did not provide a convincing hypothesis. The in vitro and in vivo mutagenicity assays yielded negative results for genotoxic potential. It is therefore recommended that, for the purpose of risk characterization, a low-dose extrapolation model be applied for human risk (Q_1^*), based on the induction of liver carcinomas in male mice. The Q_1^* for fenbuconazole is 1.54×10^{-2} $(mg/kg\ bw/day)^{-1}$ in human equivalents.

Appendix II Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PARAMETER		PERTINENT INFORMATION				
CHEMICAL		FENBUCONAZOLE				
Crop	Formulation/ type	Method/timing	Rate g a.i./ha	Number/ season	Maximum rate g a.i./ha	PHI (days)
Apricots	Indar* 75 WSP Agricultural fungicide/water soluble packets	Ground/at early red bud, at full bloom and at petal-fall	105	7	735	0
Cherries (sweet and sour)		Ground/at early red bud, at full bloom and at petal-fall				
Nectarines		Ground/at early red bud, at full bloom and at petal-fall				
Peaches		Ground/at early red bud, at full bloom, at petal-fall, and at shuck split				
Plums		Ground/at early red bud, at white popcorn stage, at full bloom and at petal-fall				
LABEL RESTRICTIONS		**Do not apply by air.** **Do not graze livestock in treated areas or feed cover crops grown in treated areas to livestock.**				

PHYSICOCHEMICAL PROPERTIES	Substance	Value
Water solubility at 20°C	Fenbuconazole (RH-7592)	3.8 ppm
Solvent solubility at 25°C mg/mL		**Solvent** **Solubility (g/100 mL)** Acetonitrile 23.1 Aromatic 200 7.7 Cyclohexanone 44.5 Ethyl acetate 15.9 Ethyl alcohol 3.9 Heptane 0.1 1-octanol 1.3
n-octanol–water partition coefficient (K_{ow}) log K_{ow}		1700 ± 300 3.22 ± 0.08 (99.5% pure)
pK_a		N/A
Vapour pressure at 25°C		0.37×10^{-7} mm HG
Relative density		N/A

NATURE OF THE RESIDUE—ANIMAL	Neither poultry nor livestock feed items are associated with the use of fenbuconazole on stone fruit. Therefore, no animal metabolism study is needed.
NATURE OF THE RESIDUE—PLANTS Radiolabelling Positions Proposed Metabolic Pathway Residue of Concern (ROC)	Peaches (Red Haven) Phenyl-labelled [^{14}C]RH-7592 and triazole-labelled [^{14}C]RH-7592 The metabolism of RH-7592 proceeded via three pathways. The first pathway was through an initial hydroxylation at benzylic carbon adjacent to the chlorophenyl ring, followed by ring closure to the iminolactone that readily hydrolysed to the lactone, RH-9129. The second pathway released free triazole, by oxidation of the carbon next to triazole ring, which led to the triazole conjugates, triazole alanine and triazole acetic acid. The third degradation pathway produced RH-4911 which led to the glucose conjugates, glucoside and malonyl glucoside of RH-4911. The parent compound (RH-7592) and its lactone metabolite that exists in the form of two stereoisomers (RH-9129 and RH-9130)
RESIDUE ANALYTICAL METHOD	Stone fruit matrices The residues of fenbuconazole and its metabolites are extracted in stone fruits using methanol. The extract is separated by filtration and then partitioned with 9.1% sodium chloride and methylene chloride. The elute is collected and evaporated to dryness, and residues are reconstituted in toluene:acetone (100:10, v:v). Further purification is achieved using silica gel and florisil column chromatography with toluene:acetone (100:30, v:v) as the eluent. The residue is collected, evaporated to dryness, redissolved in toluene:methanol (100:3, v:v) and then analyzed by gas liquid chromatography using capillary column and thermionic specific detector optimized for nitrogen selectivity.
Data Gathering Method ID	Martin, John J. (Revised by Burnett, Theodore F.) December 8, 1993. Revised Residue Analytical Method for Parent RH-7592 and its Lactone Metabolites RH-9129 and RH-9130 in Stone Fruit. Rohm and Haas Co. Technical Report No. 34-90-47R. Unpublished.
Analytes	RH-7592, RH-9129 and RH-9130
Instrument/Detector	Gas liquid chromatogram/thermionic specific detector optimized for nitrogen selectivity
Instrument Parameters	**Temperature** Column—245°C Injector—265°C Detector—300°C **Flow of Gases** Air—175 mL/min Hydrogen—4.5 mL/min Helium—18 mL/min **Bead Current** 3.3 amps (varies)
Column	SPB-608 (0.53 mm ID capillary column)
Standardization method	An external standard method was used to establish retention time, response and calibration of each analyte.
Stability of Primary and/or Secondary Standard Solutions	The standard solutions were refrigerated between analyses over a period ranging from 2 to 14 weeks. No pattern of decline in detector response with time was noted during the storage and use of the standard solutions. The standard solutions appeared to be stable during this time.
Retention Times	4.18 minutes (RH-7592); 5.24 min. (RH-9129); 5.82 min. (RH-9130)

Limit of Detection	The LOD was 0.01 ppm* for all analytes.
Limit of Quantitation	The LOQ was established at 0.05 ppm* for all analytes.
Repeatability/Precision	The analytical method obtained acceptable results by an independent laboratory validation (ILV) method for the determination of residues of RH-7592, RH-9129, and RH-9130 in stone fruit.
Reproducibility	The result of ILV indicated that analytical method (TR 34-90-47R) was reproducible.
Linearity	The method/detector response was linear (correlation coefficient, r>0.999) within the range of 0.05–1.0 ppm for RH-7592, RH-9129, and RH-9130 in stone fruit.
Specificity	The chromatographic peaks were well defined and symmetrical with no apparent carryover to the following chromatograms in the area of analytical interest for both control and spiked samples.
Multiresidue Method	Existing multiresidue methods of analysis that are currently in common usage were not found to be suitable for the determination of fenbuconazole in apricot, cherries, nectarine, peaches, plum, and prune
Storage Stability Data	The residues of RH-7592, RH-9129, and RH-9130 were stable at approximately -10°C in stone fruit for more than 54.5 months. The residues were stable for storage duration of the samples from metabolism, supervised residue trials, processing, and analytical methodology studies.

Crop Field Trials	Supervised crop field trials were conducted in the U.S. (zones 1, 1A, 2, 4, 5, 5A, 10, 11 and 12) applying five to ten times fenbuconazole (2F or Indar 75 WSP) at a single rate of 56–224 g a.i./ha, up to 2.2 kg a.i./ha/season, on apricots, cherries, peaches, plums, and prunes. The treated crops were harvested at intervals between 0 and 21 days after the final application. The proposed label rate recommends seven applications at a rate of 105 g a.i./ha for a total season rate of 735 g a.i./ha. The results from 4 trials conducted in the U.S. (zones 10 and 11) on apricots, applying 6 times at a rate of 140 g a.i./ha for a total of 840 g a.i./ha/season (1.14× the proposed label rate), indicated that the maximum combined residues of fenbuconazole and its metabolites in apricot, harvested at day 0 following the last application, were 0.268 ppm. An MRL of 0.3 ppm is recommended to cover the expected residues of fenbuconazole (RH-7592) and its lactone metabolites (RH-9129 and RH-9130) from the proposed use of Indar 75 WSP on apricots in Canada. The results from 19 trials conducted in the U.S. (zones 1, 5A and 11) on cherries, applying 6 times at a rate 112–140 g a.i./ha for a total of 672–1344 g a.i./ha/season (0.9–1.82× the proposed label rate), indicated that the maximum combined residues of fenbuconazole and its metabolites in cherries, harvested 0, 3 and 7 days following the last application, were 0.749 ppm. An MRL of 0.8 ppm is recommended to cover the expected residues of fenbuconazole and its lactone metabolites from the proposed use of Indar 75 WSP on cherries in Canada. The results from 8 trials conducted in the U.S. (zones 1, 2, 10 and 11) on peaches, applying 7 to 10 times at a rate of 112–224 g a.i./ha for a total of 784–1008 g a.i./ha/season (1.1–1.4× the proposed label rate), indicated that the maximum combined residues of fenbuconazole and its metabolites in peaches, harvested on day 0 following the last application, were 0.5 ppm. An MRL of 0.5 ppm is recommended to cover the expected residues of fenbuconazole and its lactone metabolites from the proposed use of fenbuconazole on peaches in Canada. The residue trials submitted for peaches are accepted as bridging data to support the use of Indar 75 WSP on nectarines. An MRL of 0.5 ppm is also recommended to cover the expected residues of fenbuconazole and its lactone metabolites from the proposed use of Indar 75 WSP on nectarines in Canada. The results from 8 trials conducted in the U.S. (zones 1, 5A, 10, 11 and 12) on plum and prune, applying 6 to 12 times at a rate of 56–224 g a.i./ha for a total of 672–1008 g a.i./ha/season (0.9–1.4× the proposed label rate), indicated that the maximum combined residues of fenbuconazole and its metabolites in plum and prune, harvested on day 0 following the last application, were 0.08 ppm. An MRL of 0.1 ppm is recommended to cover the expected residues of fenbuconazole and its lactone metabolites from the proposed use of fenbuconazole on plums and fresh prunes in Canada.
Residue Decline	There was some residue decline in peach after seven days of application. However, this will not affect the level of residue in stone fruits at harvest, since the proposed label suggests that Indar 75 WSP may be applied up to the day of harvest.

Processed Food	The fresh plums were processed into dry prunes. A comparison of the residues in the RAC with those in processed fruit demonstrated concentration in dry prunes. The residues of fenbuconazole and its lactone metabolites in dry prunes will be covered under the recommended MRL of 0.5 ppm.
Dairy Cattle Feeding	Neither poultry nor livestock feed items are associated with the use of fenbuconazole on stone fruit. It is expected that no residue of fenbuconazole will be present in poultry and livestock food commodities as a result of this use.
PROPOSED MRLs	Total combined residues of RH-7592, RH-9129 and RH-9130 in/on apricot (0.3 ppm); cherry (0.8 ppm); peach (0.5 ppm); nectarine (0.5 ppm); plum (0.1 ppm); fresh prune (0.1 ppm); dry prune (0.5 ppm)
United States Tolerances	Residues of RH-7592, RH-9129 and RH-9130 in/on banana (0.3 ppm); blueberry (1.0 ppm); stone fruit crop group (except plums and prune) (2.0 ppm); grapefruit (0.5 ppm), grapefruit oil (35 ppm); grapefruit dried pulp (4.0); pecan (0.1 ppm)
Codex MRLs	Residues of RH-7592, RH-9129 and RH-9130 in/on banana (0.05 ppm); cherries (1.0 ppm); cucumber (0.2 ppm); grapes (1.0 ppm); melons (except watermelon) (0.2 ppm); pecan (0.05 ppm); pomefruit (0.1 ppm); rye (0.1 ppm); summer squash (0.05 ppm); sunflower seed (0.05 ppm); wheat (0.1 ppm); wheat straw and fodder, dry (3.0 ppm)
Dietary Risk Assessment DEEM™ Version 7.72 1994–1998 Continuing Survey of Food Intakes for Individuals	For chronic risk from dietary exposure to the residues of fenbuconazole and its metabolites from food and water, the potential daily intake (PDI) was less than 3% of the acceptable daily intake (ADI) for all population subgroups including infants, children, adults and seniors. For acute dietary intake at the 95th percentile, exposure to the residues of fenbuconazole and its metabolites represented 1.87% of the ARfD for women 13+ years of age. The lifetime cancer risk from dietary exposure to the residues of fenbuconazole and its metabolites from food and water was estimated to be 1.72×10^{-6} for all infants (<1 year) and children 1–6 years, and $<8 \times 10^{-7}$ for the rest of the subgroups. It is expected that further refinement would result in a lifetime risk less than the level of concern of 1.00×10^{-6}.

* Analytical Chemistry Branch of the USEPA conducted method validation tests and noted that the sensitivity of the method under optimum operating conditions is 0.001 ppm for RH-7592 and 0.002 ppm for RH-9130 and RH-9129. The sensitivity may be increased by adjusting the current that is applied to the thermionic detector bead.

Appendix III Food Residue Chemistry Integrated Summary Table

FENBUCONAZOLE		
PLANT STUDIES		
CROPS (N=1)		Peach
ROC FOR MONITORING		RH-7592 (fenbuconazole) and its lactone metabolites, RH-9129 and RH-9130
ROC FOR RISK ASSESSMENT		RH-7592 (fenbuconazole) and its lactone metabolites, RH-9129 and RH-9130
DIETARY RISK FROM FOOD AND WATER		
Chronic non-cancer dietary risk **ADI = 0.0128 mg/kg bw**	**POPULATION**	**ESTIMATED RISK (% of ADI)**
		Median residue values; % U.S. import; % crop treated; processing factors; estimated environmental concentration for drinking water
	All infants <1 year old	2.8
	Children 1–6 years	1.8
	Children 7–12 years	0.8
	Females 13+ years	0.5
	Males 13+ years	0.4
	Seniors 55+ years	0.6
	Total population	0.7
Chronic cancer dietary risk **Q_1* = 0.0154 mg/kg bw**	**POPULATION**	**ESTIMATED LIFETIME RISK**
		Median/anticipated residue values; % U.S. import; % crop treated; processing factors; estimated environmental concentration for drinking water
	All infants <1 year old	1.72×10^{-6}
	Children 1–6 years	1.72×10^{-6}
	Children 7–12 years	7.89×10^{-7}
	Females 13+ years	4.29×10^{-7}
	Males 13+ years	4.32×10^{-7}
	Seniors 55+ years	6.25×10^{-7}
	Total population	6.26×10^{-7}

Acute dietary exposure analysis, 95th percentile ARfD = 0.01 mg/kg bw	POPULATION	ESTIMATED RISK (% of ARfD)
		Median residue values; % U.S. import; % crop treated; processing factors; estimated environmental concentration for drinking water
	Females 13+ years	1.87

Appendix IV Environmental Assessment

Table 1 Fate and Behaviour in the Terrestrial Environment

Property	Test Substance	Value	Comments
Abiotic Transformation			
Phototransformation on soil	RH-7592	DT_{50}: 79 d	Not an important route of transformation
Biotransformation			
Biotransformation in aerobic soil	RH-7592	DT_{50}: 285 d (silty clay loam) DT_{50}: 367 d (sandy loam)	This is a route of transformation, albeit a slow process. Fenbuconazole is persistent in soil under aerobic conditions.
Biotransformation in anaerobic soil	RH-7592	DT_{50}: 451 d (silty clay loam) DT_{50}: 655 d (sandy loam)	This is a route of transformation, albeit a very slow process. Fenbuconazole is persistent in soil under anaerobic conditions.

Property	Test Substance	Value	Comments
Mobility			
Adsorption/desorption in soil		Adsorption K_d (mL/g): clay: 5.1 sand: 7.6 silty clay loam: 20 loam: 75 sandy loam: 115 Adsorption K_{oc} (mL/g): clay: 2200 sand: 2600 silty clay loam: 2900 loam: 5400 sandy loam: 9000	The degree of adsorption is associated with the percentage of organic matter in soil. Fenbuconazole was slightly mobile in soils with low organic carbon content (generally ≤1%) and relatively immobile in soils with higher levels of organic carbon. Desorption values were not accepted. In the soils tested, fenbuconazole was immobile in loam and sandy loam with slight to low mobility in clay, sand, and silty clay loam.
Soil leaching—aged soil		K_{oc}: ≥3445 mL/g (sandy loam)	Fenbuconazole has a slight potential to leach in sandy loam soil.
Field Studies			
Field dissipation		DT_{50} for Ecoregion 9.2 (temperate prairies): unable to determine to >364 d DT_{50} for Ecoregion 6.2 (Western Cordillera): 198 d to >364 d	Persistent under field conditions.
Field leaching	—	—	—

Table 2 Fate and Behaviour in the Aquatic Environment

Property	Test Material	Value	Comments
Abiotic Transformation			
Hydrolysis	RH-7592	pH 5: 2210 d pH 7: 3740 d pH 9: 1340 d	Does not hydrolyze
Phototransformation in water	RH-7592	1280 d	Not a route of transformation
Biotransformation			
Biotransformation in aerobic water	Not applicable		Fenbuconazole rapidly partitions to sediment; therefore, this study is not applicable.
Biotransformation in aerobic water/sediment systems	RH-7592	River water: 3.4-4.3 d River sediment: No value River system: 906 to >1000 d (loamy sand) Pond water: 1.2 d Pond sediment: No value Pond system: 442 to >1000 d (loam)	Not an important route of transformation. The fate of fenbuconazole in aerobic water/sediment systems is partitioning to sediment. Fenbuconazole was non-persistent in water and persistent in sediment.
Biotransformation in anaerobic water/sediment systems	Not applicable	—	A request for a waiver was granted as the aquatic biotransformation behaviour is described by other studies.
Partitioning			
Adsorption/desorption in sediment	Not applicable	—	No study was submitted. Fenbuconazole partitions to sediment where it is persistent.

Property	Test Material	Value	Comments
Field Studies			
Field dissipation	Not applicable	—	No aquatic field study was submitted.

Table 3 Effects on Terrestrial Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Invertebrates				
Earthworm	Acute	RH-7592	LC_{50}: >98 mg a.i./kg dw	Non-toxic up to 98 mg a.i./kg dw
Bee	Oral	Not applicable	—	—
	Contact	RH-7592	LD_{50}: >292 µg a.i./bee NOEL not reported	Relatively non-toxic
	Brood/hive	Not applicable	—	—
Parasitic wasp *Aphidius rhopalosiphi*	Contact 68 g a.i./ha and 132 g a.i./ha	Indar 5 EW (Guarantee: 5.40%)	LD_{50}: >132 g a.i./ha NOER: 132 g a.i./ha Reduction in beneficial capacity: -11% and 1%, respectively.	Harmless at 132 g a.i./ha
Predatory mite *Typhlodromus pyri*	Contact (mortality and fecundity)	Indar 5 EW (Guarantee: 5.40%)	LR_{50}: >63 g a.i./ha NOER: 63 g a.i./ha Reduction in beneficial capacity: 9%.	Harmless at 63 g a.i./ha
	Field study 75 g a.i./ha and 150 g a.i./ha	Indar 5 EW (Guarantee: 5.40%)	LR_{50}: >150 g a.i./ha NOER: 150 gai/ha (× 9 applications) Reduction in beneficial capacity: ≤6% and 13%, respectively.	Harmless at 63 g a.i./ha

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Foliage-dwelling predator *Chrysoperla carnea*	Contact	Indar 5 EW (5.37% a.i.; 53.65 g a.i./L)	LR_{50}: >79.7 g a.i./ha NOER: 79.7 g a.i./ha Reduction in beneficial capacity: -29.4%.	Harmless at 79.7 g a.i./ha
Foliage-dwelling predator *Coccinella septempunctata*	Contact	Indar 5 EW (5.37% a.i.; 53.65 g a.i./L)	LR_{50}: >66.2 gai/ha NOER: 66.2 g a.i./ha Reduction in beneficial capacity: -13.7%.	Harmless at 66.2 g a.i./ha
Ground-dwelling predator *Poecilus cupreus*	Contact	Indar 5 EC (Guarantee: 5.37%)	LR_{50}: >76.8 gai/ha NOER: 76.8 g a.i./ha	Harmless at 76.8 g a.i./ha
Birds				
Bobwhite quail	Acute	RH-7592	LD_{50}: >2150 mg a.i./kg bw NOEL: 1470 mg a.i./kg bw	Practically non-toxic
	Dietary	RH-7592	LC_{50}: 4954 mg a.i./kg diet NOEC: 625 mg a.i./kg diet	Slightly toxic
	Reproduction	RH-7592	LOEC: 600 mg a.i./kg diet NOEC: 150 mg a.i./kg diet	—
Mallard duck	Acute	Not applicable	—	—
	Dietary	RH-7592	LC_{50}: 2013 mg a.i./kg diet NOEC: 312 mg a.i./kg diet	Slightly toxic
	Reproduction	RH-7592	LOEC: 600 mg a.i./kg diet NOEC: 150 mg a.i./kg diet	—
Mammals				
Refer to Section 3.				

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Vascular Plants				
Vascular plant	Seedling emergence	Not applicable	—	—
	Vegetative vigour	Not applicable	—	—
	Greenhouse study	RH-7592	NOEC: 750 g a.i./ha EC_{25}: >750 g a.i./ha	No phytotoxic "injury" was observed

[a]Atkins et al. (1981) for bees and USEPA classification for others, where applicable

Table 4 Effects on Aquatic Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Freshwater Species				
Daphnia magna	Acute	RH-7592	EC_{50} 2.3 mg a.i./L NOEC: 0.78 mg a.i./L	Moderately toxic
	Chronic	RH-7592	LOEC: 0.15 mg a.i./L NOEC: 0.078 mg a.i./L	—
Chironomid	Acute	Not applicable	—	—
	Subchronic	RH-7592	EC_{50} for water: 0.86 mg a.i./L EC_{50} for sediment: 12.7 mg a.i./kg sediment NOEC for water: 0.74 mg a.i./L water NOEC for sediment: 9.1 mg a.i./kg sediment	—
Rainbow trout	Acute	RH-7592	LC_{50}: 1.4 mg a.i./L NOEL: 0.7 mg a.i./L	Moderately toxic
Bluegill sunfish	Acute	RH-7592	LC_{50}: 0.68 mg a.i./L NOEC: 0.42 mg a.i./L	Highly toxic
Fathead minnow	Chronic	RH-7592	Early life stage study NOEC: 0.082 mg a.i./L LOEC: 0.16 mg a.i./L Whole life-cycle study NOEC:	—

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
			0.027 mg a.i./L LOEC: 0.045 mg a.i./L	
Freshwater algae	Acute	RH-7592	*Selenastrum capricornutum* Printz (freshwater green algae) NOEC (120 h): 0.27 mg a.i./L EC_{25} (120 h): 0.39 mg a.i./L EC_{50} (120 h): 0.48 mg a.i./L	—
Vascular plant	Dissolved	Not applicable	—	—
	Overspray	Not applicable	—	—
Marine Species				
Crustacean	Acute	RH-7592	Mysid shrimp *Mysidopsis bahia* LC_{50}: 0.63 mg a.i./L NOEC: 0.16 mg a.i./L	Highly toxic
	Chronic	Not applicable	—	—
Mollusk	Acute	RH-7592	Eastern Oyster, *Crassostrea virginica* NOEC: 0.53 mg a.i./L LOEC: 0.69 mg a.i./L	Highly toxic
	Chronic	Not applicable	—	—
Fish	Acute	RH-7592	LC_{50}: 1.8 mg a.i./L NOEC: 0.89 mg a.i./L	Moderately toxic
	Salinity challenge	Not applicable	—	—
Marine alga	Acute	Not applicable	—	—

[a]USEPA classification, where applicable

Table 5 Risk to Terrestrial Organisms

Organism	Exposure	Endpoint Value	EEC	MOS	Risk
Invertebrates					
Earthworm	Acute	98 mg a.i./kg soil	0.29 mg a.i./kg soil	340	Negligible risk
Bee	Oral	—	N/A	N/A	—
	Contact	327 kg a.i./ha	0.735 kg a.i./ha	445	Negligible risk
	Brood/hive	—	N/A	N/A	—
Predatory arthropod	Contact: Indar 5 EW and Indar 5 EC	See Table 3	105 g a.i./ha × 9 applications	N/A	Harmless (*Chrysoperla carnea* , *Coccinella septempunctata*, *Poecilus cupreus*, and *Typhlodromus pyri*)
Parasitic arthropod	Contact: Indar 5 EW and Indar 5 EC	See Table 3	105 g a.i./ha × 9 applications	N/A	Harmless (*Aphidius rhoplosiphi*)
Birds					
Bobwhite quail	Acute	1470 mg a.i./kg bw	53.5 mg a.i./kg dw	374 days*	Negligible risk
	Dietary	625 mg a.i./kg dw	53.5 mg a.i./kg dw	12	Negligible risk
	Reproduction	150 mg a.i./kg dw	53.5 mg a.i./kg dw	2.8	Low risk
Mallard duck	Acute	—	N/A	N/A	—
	Dietary	312 mg a.i./kg dw	9.5 mg a.i./kg dw	33	Negligible risk
	Reproduction	150 mg a.i./kg dw	9.5 mg a.i./kg dw	16	Negligible risk
Mammals					
Rat	Acute	400 mg a.i./kg bw	50 mg a.i./kg dw	55 days†	Negligible risk
	Dietary	20 mg a.i./kg dw	50 mg a.i./kg dw	0.4	Moderate risk
	Reproduction	80 mg a.i./kg dw	50 mg a.i./kg dw	1.6	Low risk

Organism	Exposure	Endpoint Value	EEC	MOS	Risk
Mouse	Acute	500 mg a.i./kg bw	54 mg a.i./kg dw	36 days‡	Negligible risk
	Dietary	10 mg a.i./kg dw	54 mg a.i./kg dw	0.19	Moderate risk
	Reproduction	Not applicable	N/A	N/A	—
Vascular Plants					
Vascular plant	Screening tests	750 g a.i./ha	735 g a.i./ha	>1	Expected to be negligible risk

* For bobwhite quail acute oral toxicity (DACO 9.6.2.1), food consumption (FC) was 0.015 kg dw/ind/day, body weight per individual (BWI) was 0.204 kg bw/ind. Under Wild Bird Scenario 2, the EEC was 53.5 mg a.i/kg dw. Therefore, the daily intake (DI = FC × EEC) was 0.80 mg a.i./ind/day. The $NOEL_{(ind)}$ (= NOEL × BWI) was 300 mg a.i./ind. The number of days for a wild population to reach the NOEL in the laboratory population was calculated as $NOEL_{(ind)}$/DI (= 374 d).

† For rat acute oral toxicity, the most sensitive rats were males in the end-use product study. FC was 0.028 kg dw/ind/day, BWI was 0.192 kg bw/ind. Under Wild Mammal Scenario 2, the EEC was 50 mg a.i./kg dw. Therefore, the daily intake (DI = FC × EEC) was 1.4 mg a.i./ind/day. The $NOEL_{(ind)}$ (= NOEL × BWI) was 76.8 mg a.i./ind. The number of days for a wild population to reach the NOEL in the laboratory population was calculated as $NOEL_{(ind)}$/DI (=55 d).

‡ For mouse acute oral toxicity, the most sensitive mice were females. Food consumption (FC) was 0.006 kg dw/ind/day, body weight per individual (BWI) was 0.023 kg bw/ind. Under Wild Mammal Scenario 2, the EEC was 54 mg a.i./kg dw. Therefore, the daily intake (DI = FC × EEC) was 0.32 mg a.i./ind/day. The $NOEL_{(ind)}$ (NOEL × BWI) was 11.5 mg a.i./ind. The number of days for a wild population to reach the NOEL in the laboratory population was calculated as $NOEL_{(ind)}$/DI (= 36 d).

Table 6 Risk to Aquatic Organisms

Organism	Exposure	Endpoint Value	EEC	MOS	Risk
Freshwater Species					
Daphnia magna	Acute	0.78 mg a.i./L	0.05 mg a.i./L	16	Negligible risk
	Chronic	0.078 mg a.i./L	—	N/A	No classification
Chironomid	Subchronic	0.74 mg a.i./L	Not determined	—	Not determined
Rainbow trout	Acute	0.7 mg a.i./L	0.05 mg a.i./L	14	Negligible risk
	Chronic	—	N/A	N/A	—
Bluegill sunfish	Acute	0.42 mg a.i./L	0.05 mg a.i./L	8.3	Low risk
	Chronic	—	N/A	N/A	—

Organism	Exposure	Endpoint Value	EEC	MOS	Risk
Fathead minnow	Chronic (early-life stage toxicity)	0.082 mg a.i./L	0.05 mg a.i./L	1.6	Low risk
	Chronic (whole life-cycle toxicity)	0.027 mg a.i./L	N/A	N/A	Endpoints affected included time to first spawn, number of eggs produced, survival of parents and offspring as well as number of eggs per spawn.
Freshwater algae	Acute	0.27 mg a.i./L	0.05 mg a.i./L	5.4	Low risk
Vascular plant	Dissolved	Incomplete data	N/A	N/A	Not determined
	Overspray	Incomplete data	N/A	N/A	Not determined
Marine Species					
Crustacean	Acute	0.16 mg a.i./L	0.05 mg a.i./L	3.2	Low risk (Result should be interpreted with caution for benthic species.)
	Chronic	—	N/A	N/A	—
Mollusk	Acute	0.53 mg a.i./L	0.05 mg a.i./L	11	Negligible risk (Result should be interpreted with caution for benthic species.)
	Chronic	—	N/A	N/A	—
Sheepshead minnow	Acute	0.89 mg a.i./L	0.05 mg a.i./L	19	Negligible risk
Salmonid	Acute	—	N/A	N/A	—
	Salinity challenge	—	N/A	N/A	—
Marine algae	Acute	—	N/A	N/A	—

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